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(54) New 7beta-substituted-4-aza-5a-androstan-3-ones as 5a-reductase inhibitors

Neue 7-Beta-substituierte-4-Aza-5-Alpha-Androstan-3-Onen als Inhibitoren 5-Alpha-Reduktases

Nouveaux 4-aza-5-alpha-androstan-3-ones-7-bêta substitués comme inhibiteurs de 5-alpha réductase

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EP-A- 0 414 529 **US-A- 4 377 584**

- **JOURNAL OF MEDICINAL CHEMISTRY vol. 29, no. 11, November 1986, WASHINGTON US pages 2298 - 2315 G. H. RASMUSSON ET AL 'Azasteroids: Structure Activity Relationships for Inhibition of 5-alpha-Reductase and of Androgen Receptor Binding'**
- **STEROIDS: STRUCTURE, FUNCTION, AND REGULATION vol. 47, no. 1, January 1986, STONEHAM, MA US pages 1 - 19 J. R. BROOKS ET AL '5-alpha-Reductase Inhibitory and Anti-Androgenic Activities of Some 4-Aza-Steroids In The Rat'**
- **J. MED. CHEM. VOL37(23) PP 3871-3874 (1994)**

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EP 0 572 166 B1

Description

BACKGROUND OF THE INVENTION

The present invention is directed to new 7β-substituted-4-aza-5α-androstan-3-ones and related compounds and the use of such compounds as 5α-reductase inhibitors.

DESCRIPTION OF THE PRIOR ART

The art reveals that certain undesirable physiological manifestations, such as acne vulgaris, seborrhea, female hirsutism, male pattern baldness and benign prostatic hypertrophy, are the result of hyperandrogeneic stimulation caused by an excessive accumulation of testosterone or similar androgenic hormones in the metabolic system. Early attempts to provide a chemotherapeutic agent to counter the undesirable results of hyperandrogenicity resulted in the discovery of several steroidal antiandrogens having undesirable hormonal activities of their own. The estrogens, for example, not only counteract the effect of the androgens but have a feminizing effect as well. Non-steroidal antiandrogens have also been developed, for example, 4'-nitro-3'-trifluoromethylisobutyranilide. See Neri, et al., Endo., Vol. 91, No. 2 (1972). However, these products, though devoid of hormonal effects, are peripherally active, competing with the natural androgens for receptor sites, and hence have a tendency to feminize a male host or the male fetus of a female host.

It is now known in the art that the principal mediator of androgenic activity in some target organs is 5α'-dihydrotestosterone, and that it is formed locally in the target organ by the action of testosterone-5α-reductase. It is also known that inhibitors of testosterone-5α-reductase will serve to prevent or lessen symptoms of hyperandrogenic stimulation.

A number of 4-aza steroid compounds are known in the art as 5α-reductase inhibitors. For example, See U.S. Patent Nos. 4,377,584, 4,220,775, 4,859,681, 4,760,071 and the articles J. Med. Chem. 27, p. 1690-1701 (1984) and J. Med. Chem. 29, 2998-2315 (1986) of Rasmusson, et al., U.S. Patent 4,845,104 to Carlin, et al., and U.S. Patent 4,732,897 to Cainelli, et al. describe 4-aza-17β- substituted-5α-androstan-3-ones which are said to be useful in the treatment of DHT-related hyperandrogenic conditions.

However, despite the suggestion in the prior art that hyperandrogeneic diseases are the result of a single 5α-reductase, there are reports regarding the presence of other 5α-reductase isozymes in both rats and humans. For example, in human prostate, Bruchovsky, et al. (See J. Clin. Endocrinol. Metab. 67, 806-816, 1988) and Hudson (see J. Steroid Biochem. 26, p 349-353, 1987) found different 5α-reductase activities in the stromal and epithelial fractions. Additionally, Moore and Wilson described two distinct human reductases with peaks of activities at either pH 5.5 or pH 7-9. (See J. Biol. Chem. 251, 19, p. 5895-5900, 1976.)

Recently, Andersson and Russell isolated a cDNA which encodes a rat liver 5α-reductase (see J. Biol. Chem. 264 pp. 16249-55 (1989). They found a single mRNA which encodes both the liver and prostatic reductases of rats. The sequence of this rat gene was later used to select a human prostatic cDNA encoding a 5α-reductase termed "5α-reductase 1". (See Proc. Nat'l. Acad. Sci. 87, p. 3640-3644, 1990.)

More recently, a second, human prostatic reductase (5α-reductase 2) has been cloned with properties identified with the more abundant form found in crude human prostatic extracts. (See Nature, 354, p. 159-161, 1991.)

Further, "Syndromes of Androgen Resistance" - The Biology of Reproduction, Vol. 46, p. 168-173 (1992) by Jean O. Wilson indicates that the 5α-reductase 1 enzyme may be associated with hair follicles.

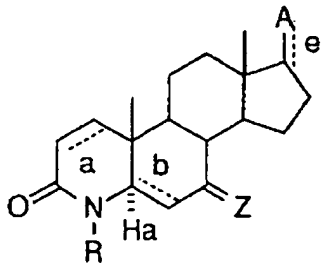
Thus, the art supports the existence of at least two genes for 5α-reductase and two distinct isozymes of 5α-reductase in humans. Both forms are present in prostatic tissue although 5α-reductase 2 is the more abundant. The other isozyme, 5α-reductase 1, is believed to be more abundant in scalp tissue.

In the treatment of hyperandrogenic disease conditions, e.g. benign prostatic hyperplasia (BPH) it would be desirable to have one drug entity which is active against both isozymes 1 and 2 in the prostate to substantially inhibit dihydrotesterone (DHT) production. Alternatively, it would be desirable to have a drug entity which is highly selective for inhibiting the scalp-associated enzyme 5α-reductase 1, for use in treating diseases of the skin and scalp, e.g. acne and alopecia. This latter drug could also be used in combination with PROSCAR® (finasteride) which is highly selective for the prostatic enzyme 5α-reductase 2 for combination therapy in the treatment of BPH.

SUMMARY OF THE INVENTION

The present invention discloses novel 7β-substituted-4-aza-5α-androstan-3-one compounds which are useful for inhibiting the 5α-reductase isozymes 1 and/or 2 and are particularly effective in selectively inhibiting the 5α-reductase 1 associated with the scalp and indually inhibiting both isozymes 1 and 2 in the treatment of benign prostatic hyperplasia, acne, female hirsutism, male pattern baldness, androgenic alopecia, prostatitis, and the prevention and treatment of prostatic carcinoma.

In accordance with the present invention there is provided novel 7β-substituted-4-aza-5α-androstan-3-one compounds of the formula:

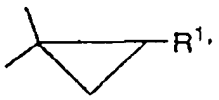


General Formula I

wherein

R is selected from hydrogen, methyl or ethyl; the dashed lines-a, b, e indicate double bonds which can be present, providing that if double bond b is present, then the 5α hydrogen, Ha, is not present;
Z is selected from:

1) oxo,
2) a-hydrogen and a β-substituent selected from C_1-C_4 alkyl, C_2-C_4 alkenyl, -CH_2COOH, hydroxy, carboxy, $COOC_1$-C_4 alkyl esters; $OCONR^1R^2$, where R^1 and R^2 are independently H, C_1-C_4 alkyl, phenyl, benzyl, and where R^1 and R^2 together with the nitrogen can form a 5-6 membered saturated heterocyclic ring, optionally with one other heteroatom; OC_1-C_4 alkyl, OC_3-C_6 cycloalkyl, -$OCOCH_3$, halo, halo C_1-C_2 alkyl, or trifluoromethyl, C_3-C_6 cycloalkyl;
3) = CH-R^1 where R^1 is H, C_1-C_4 alkyl;
4) Spiro



where R^1 is H, C_1-C_4 alkyl; and
A is -$(CHR^1)_n$-XR^4;
n is 1-10;
X is -O- or -$S(O)_p$-,
wherein p is zero, 1 or 2; and
R^1 can be the same or different when n is greater than 1 and is -H, aryl, or -C_{1-3}alkyl unsubstituted or substituted with C_6-C_{10} aryl;
R is -H, methyl or ethyl;
R^4 is 1) hydrogen or -C_{1-20} alkyl, unsubstituted or substituted with one or more of:

a) -OH,
b) halo,
c) -C_{1-8} alkoxy,
d) -C_{1-6} alkenyl,
e) -$CONR^5R^5$, wherein R^5 is independently

i) -H,
ii) -C_{1-8} alkyl unsubstituted or substituted with one or more of R^7, aryl or heterocyclic, defined below, the aryl being unsubstituted or substituted with one or more of R^7 or R^9,
iii) aryl unsubstituted or substituted with one or more of R^7 or R^9, or

iv) heterocyclic, defined below, unsubstituted or substituted with one or more of R^7 or R^9,

f) $-COOR^6$, wherein R^6 is

i) -H,
ii) $-C_{1-8}$ alkyl unsubstituted of substituted with one or more of R^7 or aryl, the aryl being unsubstituted or substituted with one or more of R^7 or R^9, or
iii) aryl, unsubstituted or substituted with one or more of R^7 or R^9,

g) $-S(O)_p-R^5$, wherein p is defined above,
h) $-N(R^5)_2$,
i) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9,
j) heterocyclic, unsubstituted or substituted with one or more of R^7 or R^9,
k) $-C_{3-10}$ cycloalkyl, unsubstituted or substituted with one or more of R^7 or R^9, or

1) $-CONR^8-CO-NHR^8$, wherein R^8 is -H, $-C_{1-8}$ alkyl, benzyl or cyclohexyl; or
2) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9, or
3) heterocycle or $-C_{3-10}$ cycloalkyl, either of which is unsubstituted or substituted with one or more of R^7 or R^9;
R^7 is

1) -CN,
2) $-C_{1-3}$ alkoxy,
3) -CN,
4) $-COOR^6$
5) $-C_{1-8}$alkyl-$COOR^6$
6) $-NO_2$, or
7) -halo; and
8) amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino;

R^9 is

1) $-C_{1-8}$ alkyl, unsubstituted or substituted with one or more of aryl or R^7,
2) -CO-A, $-C_{1-8}$ alkyl-CO-A, -NHCO-A, or $-S(O)_p-A$, wherein p is defined above and A is

a) -H,
b) $-C_{1-8}$ alkyl, unsubstituted or substituted with one or more of

i) $-R^7$, or
ii) aryl, unsubstituted or substituted with one or more of R^7, or

c) aryl, unsubstituted or substituted with one or more of R^7,

3) -NHCO-heterocyclic,
4) $-N(R^{10})_2$ or $-CON(R^{10})_2$ wherein R^{10} is independently -H, heterocyclic, or -A,
5) $-NHCO-(CH_2)_q-CO-Q$, wherein q is 1-4, and Q is $-N(R^{10})_2$ or $-OR^{10}$;

and pharmaceutically acceptable salts thereof.

Also disclosed are processes for their preparation, pharmaceutical formulations comprising the novel compounds as active ingredients and methods of inhibiting prostatic and scalp 5α-reductases in diseases which occur under hyperandrogenic conditions, e.g. benign prostatic hyperplasia, with the novel compounds and their pharmaceutical formulations.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

The following is a detailed description of the 7-position radical Z as used herein.

By the term "C_1-C_4 alkyl" as used herein, is meant to include: e.g. methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl and t-butyl.

By the term "C_2-C_4 alkenyl" as used herein is meant to include: vinyl, allyl, 1-propen-1-yl, 1-propen-2-yl, 1-buten-

1-yl, 1-buten-2-yl, and the like.

By the term "C_3-C_6 cycloalkyl" as used herein is meant to include: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

By the term "halo" as used herein is meant to include: fluoro, chloro, bromo, iodo.

By the term "OC_1-C_4 alkyl" as used herein is meant to include: methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, t-butoxy.

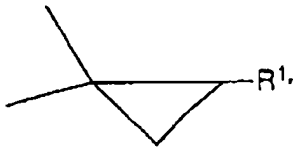
By the term "OC_3-C_6 cycloalkyl" as used herein is meant to include: cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy.

Representative examples of Z are where a-substituent (dashed lines) is hydrogen and the beta substituent (wedge) is e.g. methyl, ethyl, propyl, allyl, carboxymethyl, hydroxy, methoxy, ethoxy, cyclopropyloxy, cyclopentyloxy, acetoxy, fluoro, chloro, bromo, trifluoromethyl, trichloromethyl, fluoromethyl, chloromethyl, carboxy, N,N-dimethylcarbamoyl, hydroxymethyl, methoxymethyl, and the like.

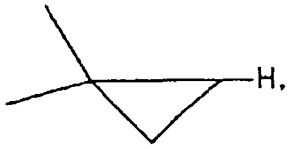
Representative examples where Z is an alkenyl substituent, =CH-R', includes, e.g. $=CH_2$, $=CH-CH_3$, $=CH-CH_2CH_3$, and the like.

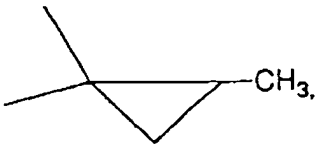
Representative examples where R^1, R^2 and the N can form a heterocyclic ring include: N-morpholinyl, N-(4-methyl) piperazinyl, N-piperidinyl, and the like.

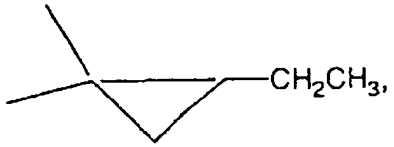
Representative examples where Z is the spiro substituent:



includes:





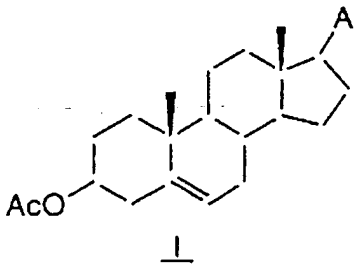


stereoisomers thereof and the like.

Unless otherwise indicated the 17-position substituent is assumed to be in the beta configuration.

The first group of preferred compounds of this invention can be made by procedures outlined in the following Flowsheets:

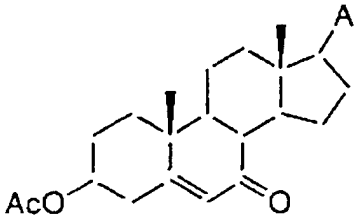
GENERAL FLOWSHEET I



I

$Cr(CO)_6$/t-BuOOH

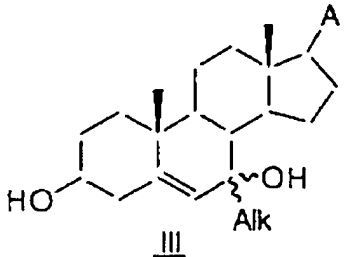
CH_3CN/Δ/reflux



II

Alk Mg Cl

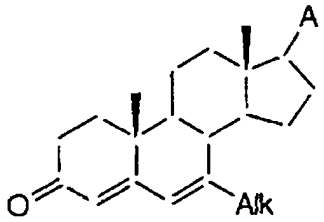
THF/24h



III

$Al(OiPr)_3/C_6H_{10}O/$

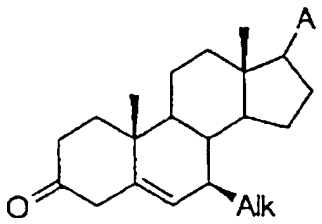
Toluene/Δ/reflux



IV

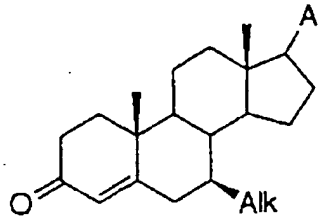
Li/THF/NH_3/Toluene/-78°

GENERAL FLOWSHEET I (CONT'D)



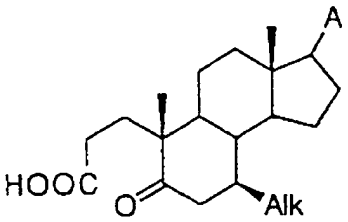
V

THF/DBU/1h
reflux



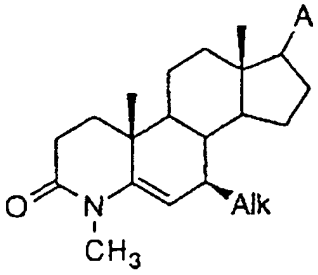
VI

$KMnO_4/NaIO_4$/t-Bu-OH/
80°/H_2O/Na_2CO_3/2h



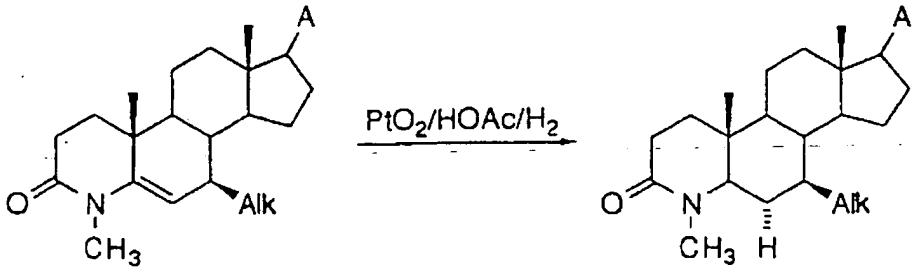
VII

NaOAc
CH_3NH_3Cl/
$CH_2OHCH_2OH\Delta$

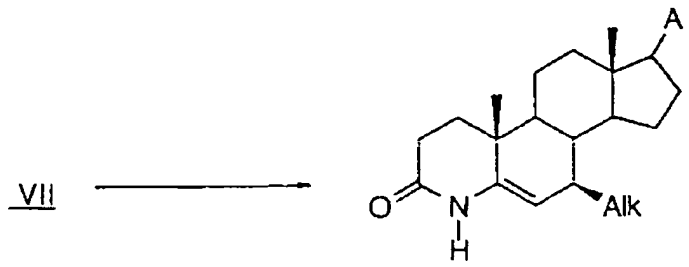


VIII

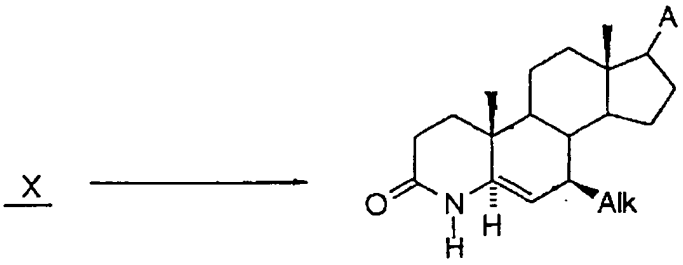
GENERAL FLOWSHEET I (CONT'D)



VIII IX



X



XI

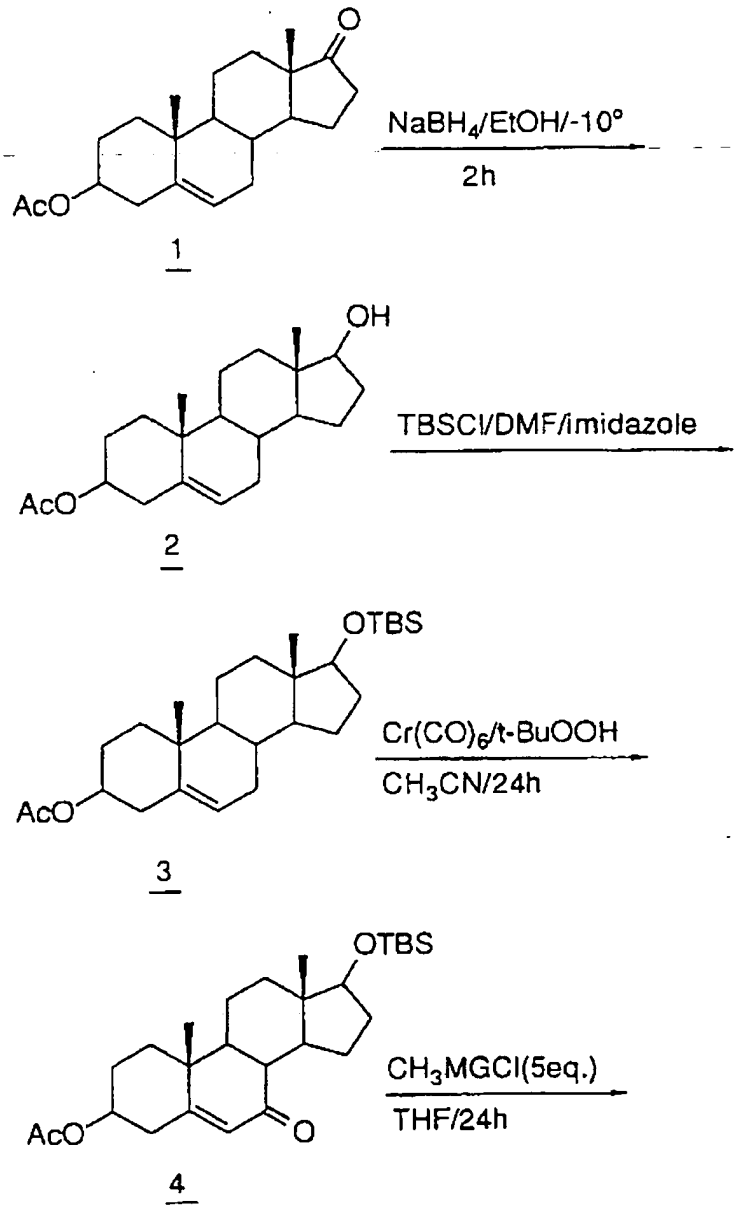
7-Beta Alkyl-17-A Series

The compounds of the instant invention comprising Z as a 7β alkyl group, e.g. methyl, ethyl, isopropyl, where A is defined above, can be prepared by the procedure outlined in The General Flowsheet.

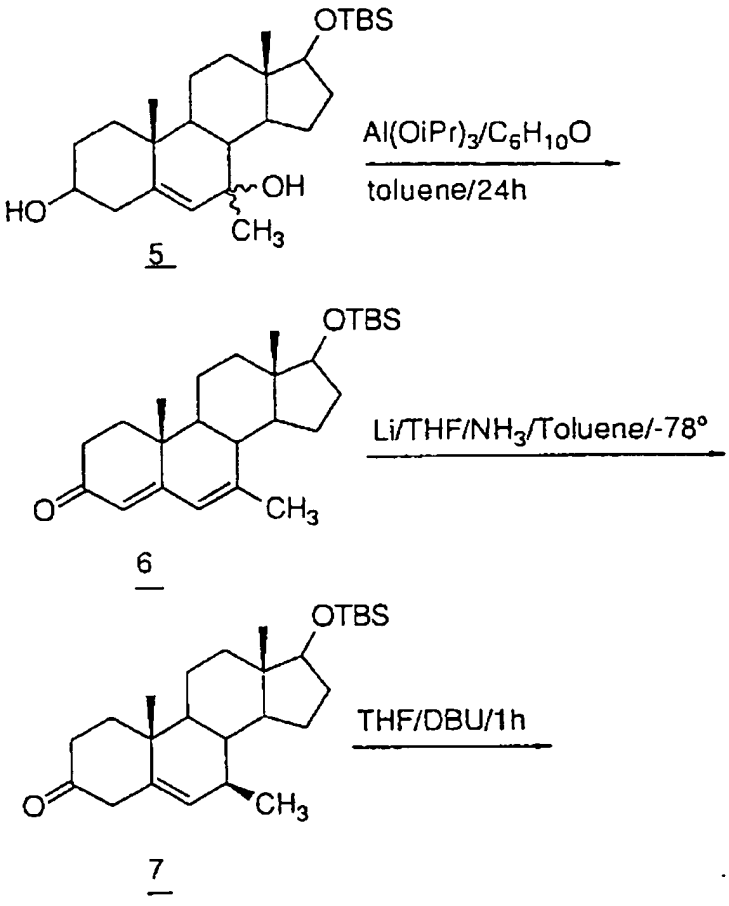
As seen in the Flowsheet, the 3-acetoxy-androst-5-en-17-A I is oxidized to the corresponding 5-en-7-one II by treatment with hydrogen t-butyl peroxide and chromium hexacarbonyl in e.g. acetonitrile, at reflux. The C_1-C_4 alkyl group, designated Alk, e.g. methyl, can be introduced at this point by a Grignard reaction using e.g., alkyl magnesium chloride in e.g., anhydrous THF at 0-10°C to produce the 7-alkyl-7-hydroxy adduct III. This is then oxidized with e.g. aluminum isopropoxide and cyclohexanone (Oppenauer oxidation conditions) in refluxing toluene solvent to produce the 7-alkyl-4,6-dien-3-one IV. This in turn is reduced via a e.g., metal-ammonia reduction, using e.g., lithium, liquid ammonia, THF and toluene at -78°C to selectively yield the 7-beta-alkyl-5-en-3-one V. In the next step the delta-5 double bond is isomerized to the 4-ene by use of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in, e.g. refluxing tetrahydrofuran (THF) to produce the 7-alkyl 4-en-3-one, VI. The A Ring is next cleaved by treatment with e.g. potassium permanganate, sodium periodate in t-butyl alcohol at 80°C to produce the corresponding seco-acid VII. Treatment of the seco-acid with an appropriate amine e.g., methylamine hydrochloride and sodium acetate in ethylene glycol at 180°C, yields e.g., the 4-methyl-4-aza-androst-5-en-3-one VIII. This in turn is selectively reduced with e.g., PtO_2, to remove the 5- double bond to produce the 5α-hydrogen compound IX. The seco-acid VII can be similarly treated with ammonia to produce the corresponding N-H compound, X, which can then be analogously treated with PtO_2 to produce the corresponding 5α-4N-H compound XI.

Throughout this series of reactions, the 17-A group should be inert to the individual reaction conditions and can be practiced with all of the herein disclosed 17-A side chains. There is now presented a sub-series of flowsheets denoted letter A through letter I.

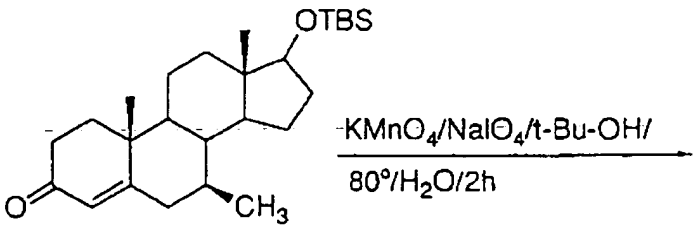
FLOWSHEET A


O
AcO
NaBH4/EtOH/-10°
2h
1
OH
AcO
TBSCl/DMF/imidazole
2
OTBS
AcO
Cr(CO)6/t-BuOOH
CH3CN/24h
3
OTBS
AcO
O
CH3MGCl(5eq.)
THF/24h
4

FLOWSHEET A (CONT'D)



FLOWSHEET A (CONT'D)



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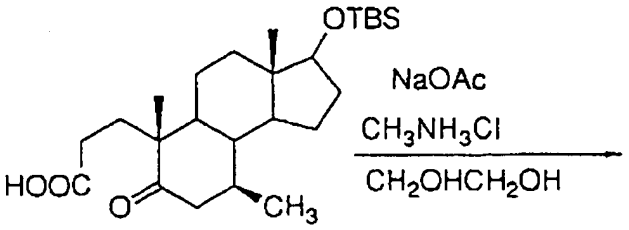

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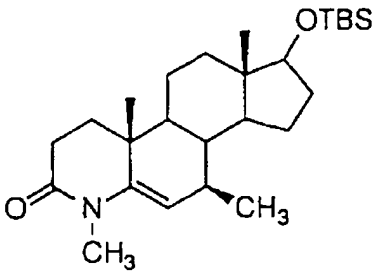
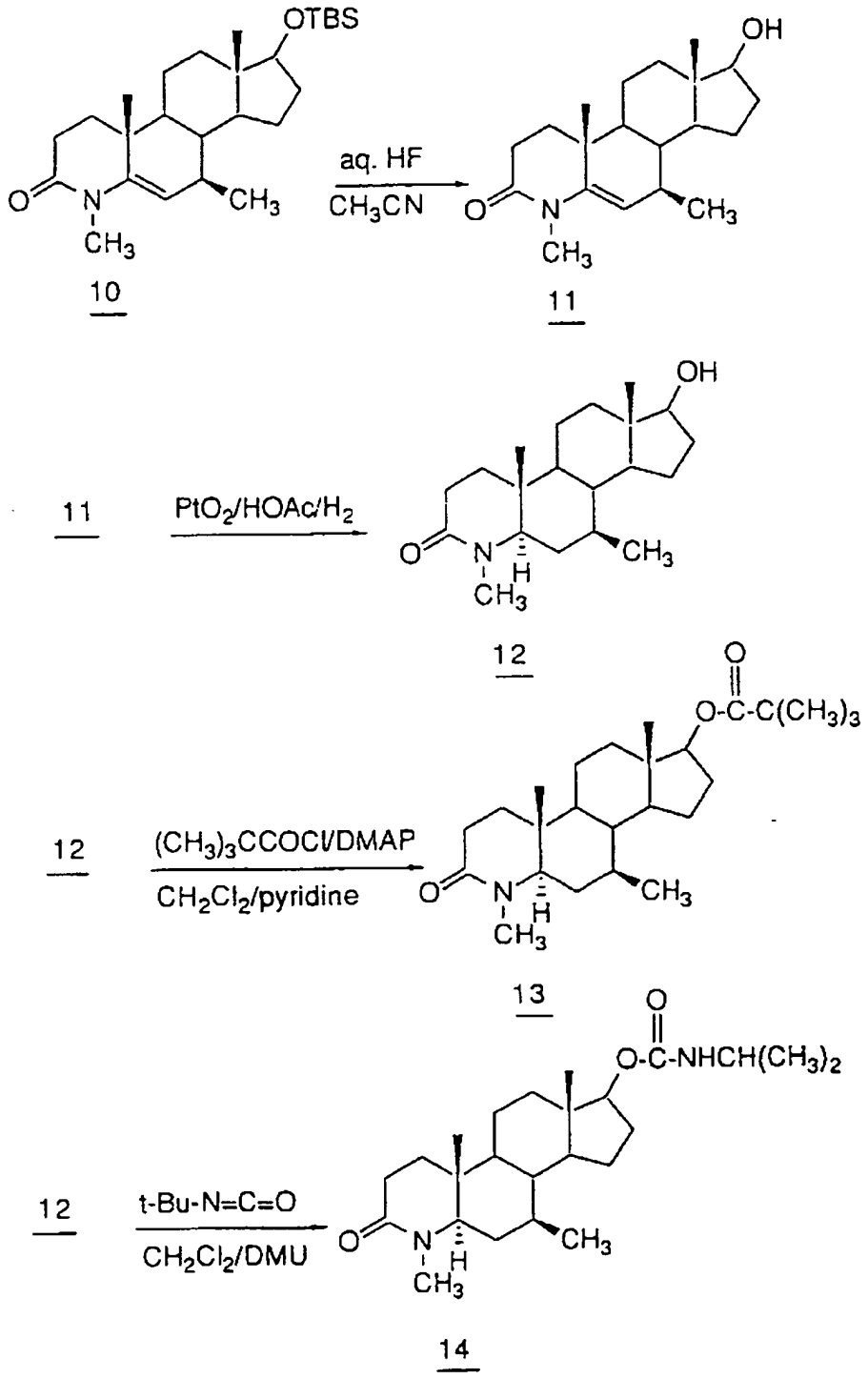


10

FLOWSHEET B


OTBS
OH
aq. HF
CH3CN
10
11
PtO2/HOAc/H2
12
(CH3)3CCOCl/DMAP
CH2Cl2/pyridine
13
t-Bu-N=C=O
CH2Cl2/DMU
14

7-Beta Alkyl-17-Oxy-Androstanes

Illustrative compounds where A is hydroxy or derivatised hydroxy and Z is an 7β alkyl group, e.g. methyl, ethyl, propyl or isopropyl, or allyl,can be prepared by the procedure outlined in Flowsheets A and B.

As seen in Flowsheet A, the 3-acetoxy-androst-5-en-17-one 1 is reacted with sodium borohydride in a suitable solvent, e.g. ethanol, at -10°C to stereospecifically reduce the 17-ketone to the 17β-ol 2. The 17-hydroxy group is protected with the TBS group (t-butyldimethyl-silyl) by reacting TBS chloride with 2 in a suitable solvent, e.g. DMF in the presence of the proton acceptor, e.g. imidazole, at room temperature, to form 3.

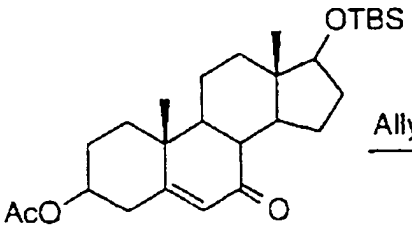
Following the hydroxy protection, this compound is oxidized in the seven position to the corresponding 5-en-7-one 4 by treatment of 3 with hydrogen t-butyl peroxide and chromium hexacarbonyl in e.g. acetonitrile, at reflux. The alkyl group, e.g. methyl, can be introduced at this point by a Grignard reaction using e.g., methyl magnesium chloride in anhydrous THF at 0-10°C to produce the 7-methyl-7-hydroxy adduct 5. This Grignard product is then oxidized with aluminum isopropoxide and cyclohexanone (Oppenauer oxidation conditions) in refluxing toluene solvent to produce the 7-methyl-4,6-dien-3-one 6. This in turn is reduced via a metal-ammonia reduction using lithium in liquid ammonia, THF and toluene at -78°C to selectively yield the 7-beta-methyl-5-en-3-one 7. In the next step the 5-double bond is isomerized to the 4-ene by use of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in refluxing tetrahydrofuran (THF) to produce the 4-en-3-one, 8. The A Ring is next cleaved by treatment with potassium permanganate, sodium periodate in t-butyl alcohol at 80°C to produce the corresponding seco-acid 9. Treatment of the seco-acid 9 with an appropriate amine e.g., methylamine hydrochloride and sodium acetate in ethylene glycol at 180°C, yields the 4-aza-androst-5-en-3-one 10. The TBS protecting group is then removed e.g., by aqueous HF in acetonitrile at 0°C, to yield the 17-β alcohol 11. This in turn is selectively reduced to remove the 5-double bond to produce the 5α-hydrogen compound 12. At this point, the 17β hydroxy group can be derivatized with a variety of reagents. For example, it can be esterified with an acid moiety, e.g. t-butyl acid chloride in a solvent, e.g., pyridine, to produce the t-pentanoic acid ester 13.

Further, 12 can be reacted with an isocyanate, e.g. t-butyl-isocyanate in a solvent and in the presence of DBU to yield the urethane ester 14.

Similarily, other acylating agents obvious to one skilled in the art can be used to derivatize the 17-beta-ol grouping.

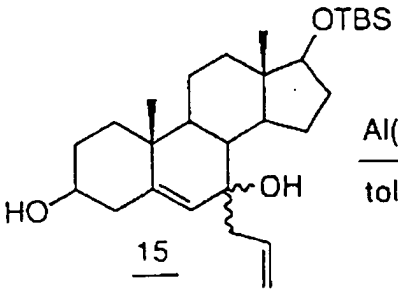
Carrying out the above series of reactions but using, e.g. ethyl magnesium chloride as the Grignard reagent, leads to the corresponding 7-beta ethyl analogs.

FLOWSHEET C



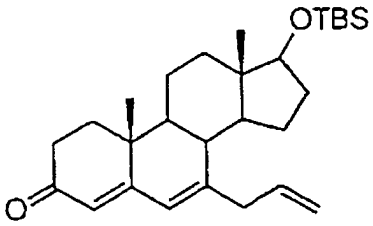
4

AllylMgBr(5 eq.)/
24h



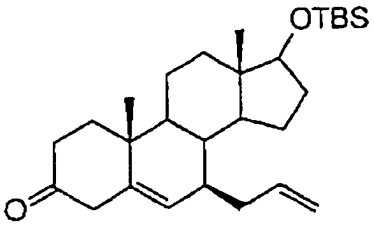
15

$Al(OiPr)_3/C_6H_{10}O$
toluene/24h



16

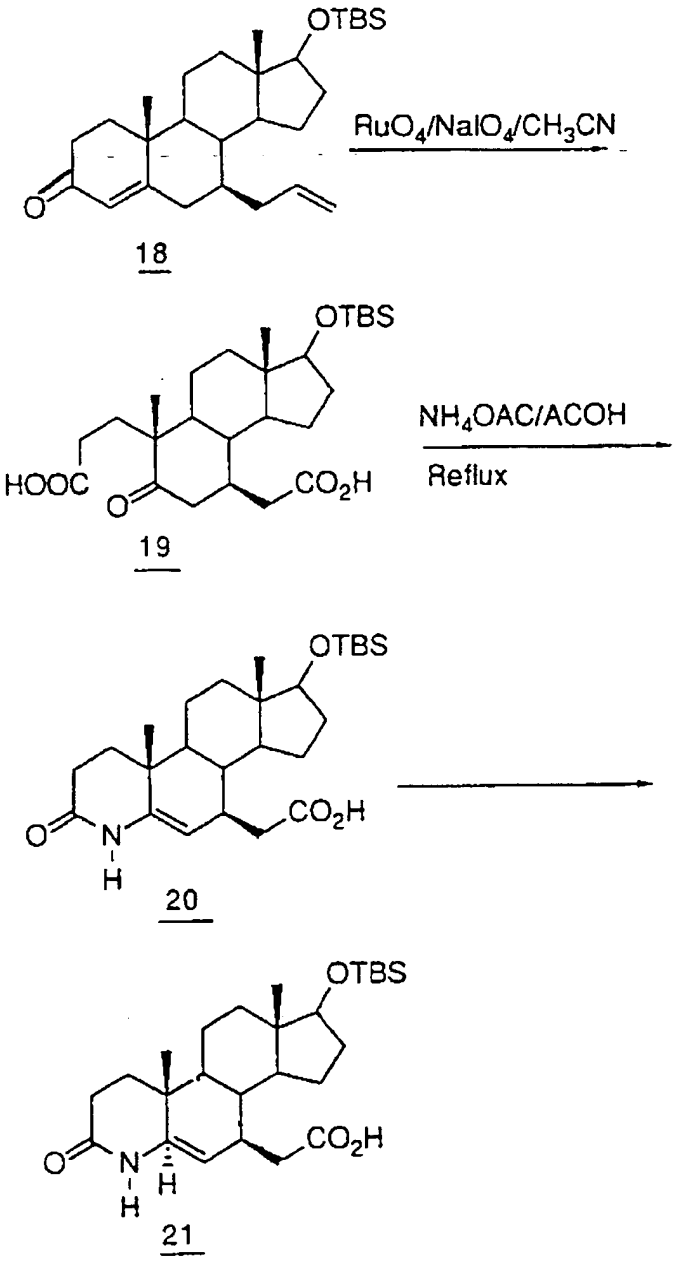
Li/THF/NH_3/
Toluene/-78°/2h



17

DBU/THF

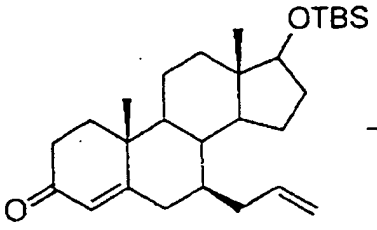
FLOWSHEET C (CONT'D)



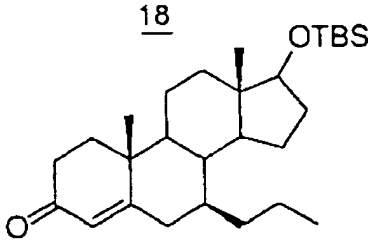
7-Carboxymethyl-17-OTBS Series (illustrative)

The 7-carboxy substituent is formed through the corresponding 7-allyl group. As seen in Flowsheet C, acetate 4 is reacted with allyl Grignard reagent to form the adduct 15 which is oxidized to the dienone 16 by Oppenauer oxidation conditions. Metal-ammonia reduction affords the 5-ene analog 17, followed by DBU-catalyzed double bond isomerization to 18. This in turn is oxidized in a key step with potassium permanganate, sodium periodate in t-butanol to form the 7-carboxymethyl seco-acid 19. Treatment with amines, e.g. ammonium salts, forms the 4-aza derivative, 20 which is then reduced to the 5-alpha 21. Use of methylamine in place of ammonia yields the corresponding 4-methyl analogs of 20 and 21.

FLOWSHEET D



18



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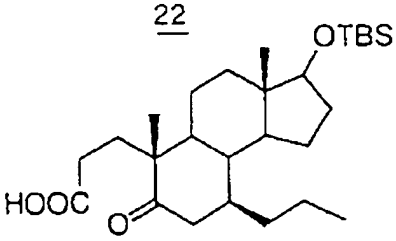

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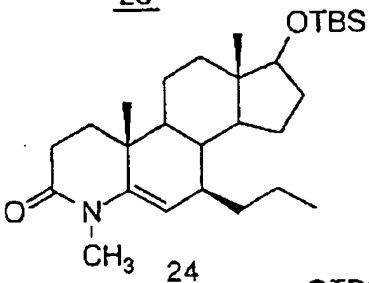

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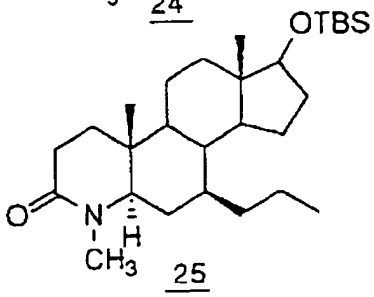
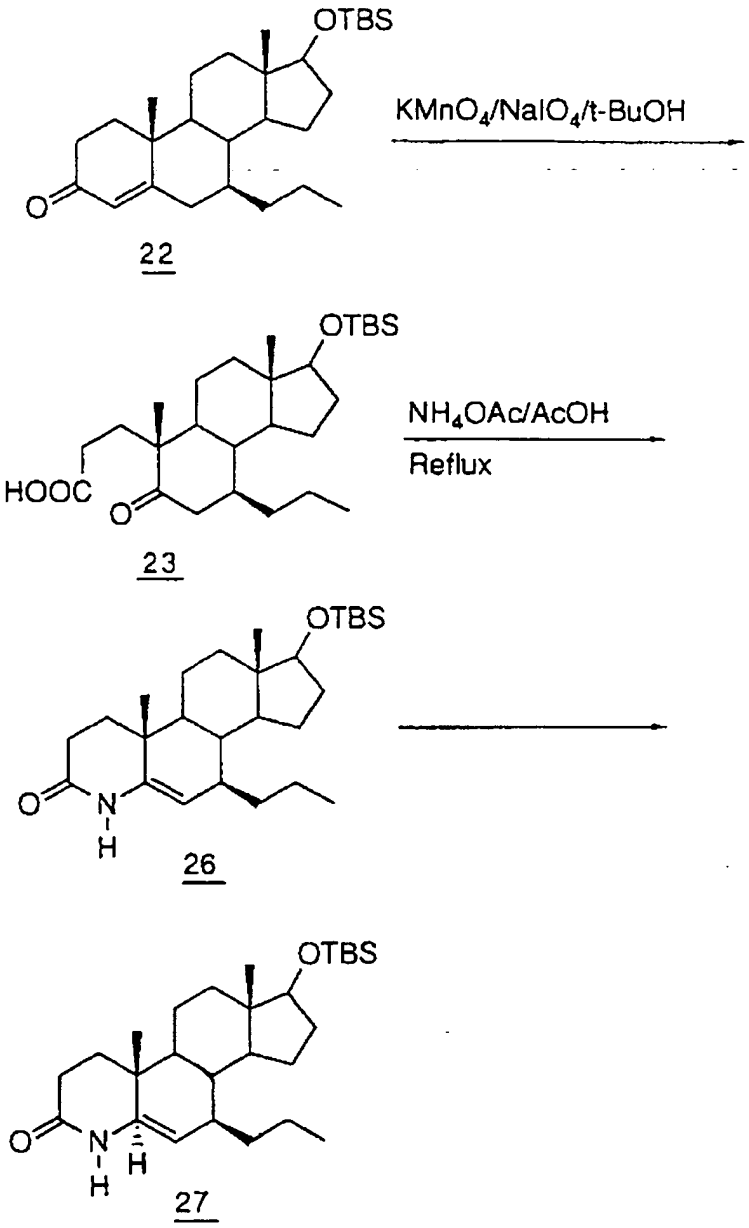


25

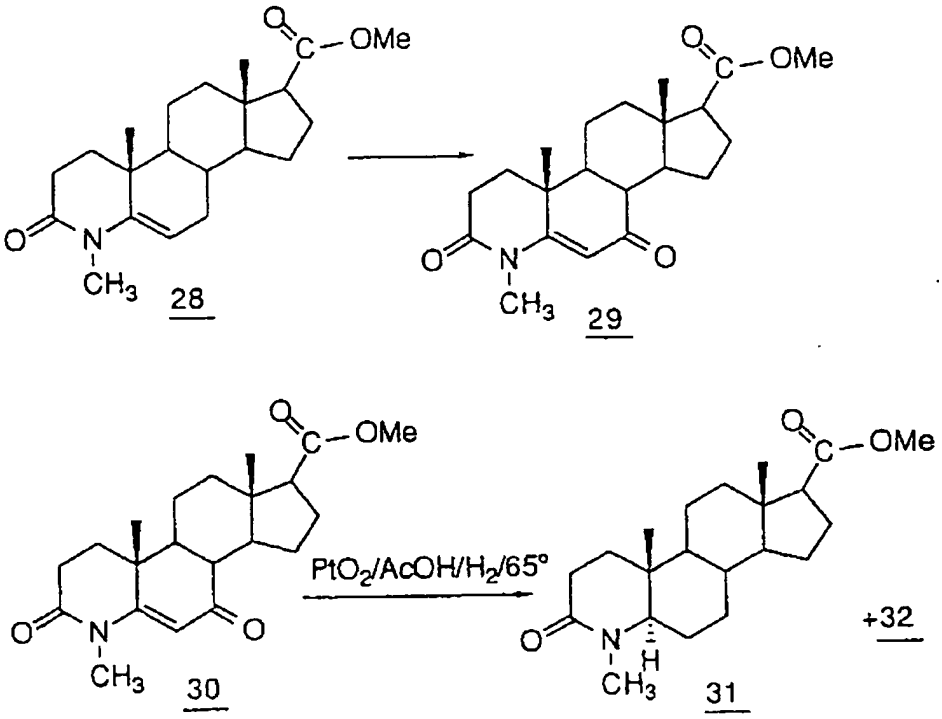
FLOWSHEET E



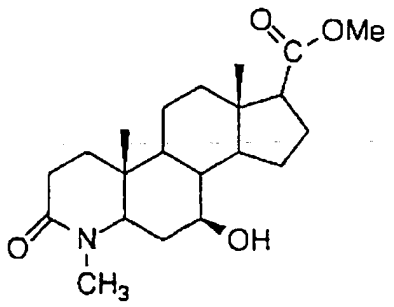
7-Propyl-17-OTBS Series (illustrative)

The 7-propyl analogs are made as illustrated in Flowsheet D starting with the 7-allyl-4-en-3-one 18, which is reduced by Wilkinson's catalyst to the propyl derivative 22, oxidized to the seco-acid 23, then condensed with amines, e.g. methylamine, to form the 4-methyl analog 24 and then reduced to the 5-alpha 25. Corresponding treatment with ammonia is shown in Flowsheet E shows the corresponding unsubstituted 4-aza 26 and 5-alpha 27 analogs.

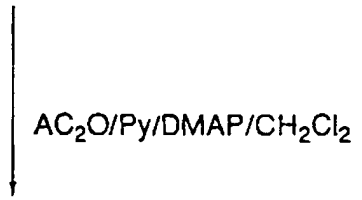
FLOWSHEET F

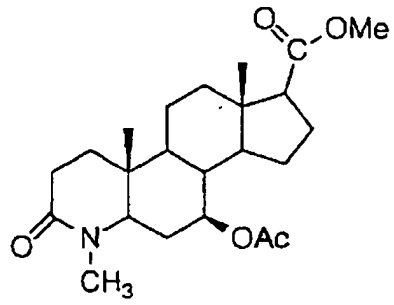


FLOWSHEET G



32



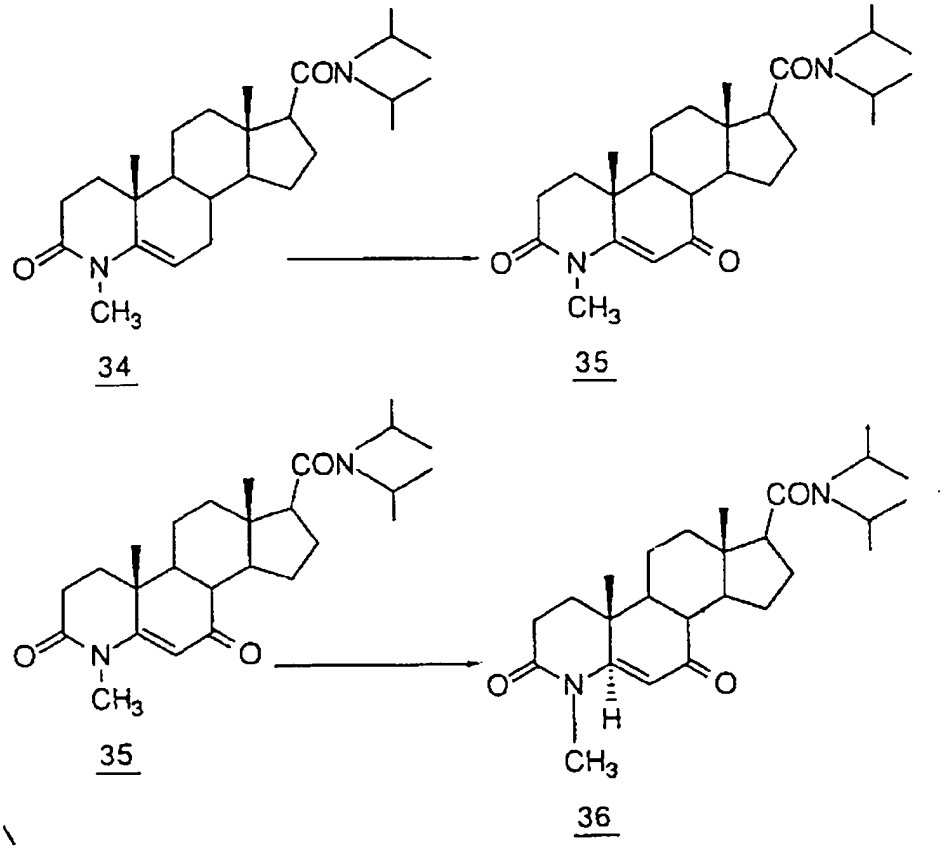


33

7-Beta Acetoxy 17-carboxyester Series

The 7-beta acetoxy series is prepared as illustrated in Flowsheets F and G by the oxidation of starting ester 28 to the 5-en-7-one 29 by the chromiumhexacarbonyl/t-butylhydroperoxide/-acetonitrile procedure described above. Platinum catalyzed hydrogenation of 29 yields two products, the fully reduced 7-H compound 31, and 7-beta hydroxy compound 32. Acylation of 32 with acetic anhydride yields the 7-beta acetoxy compound 33.

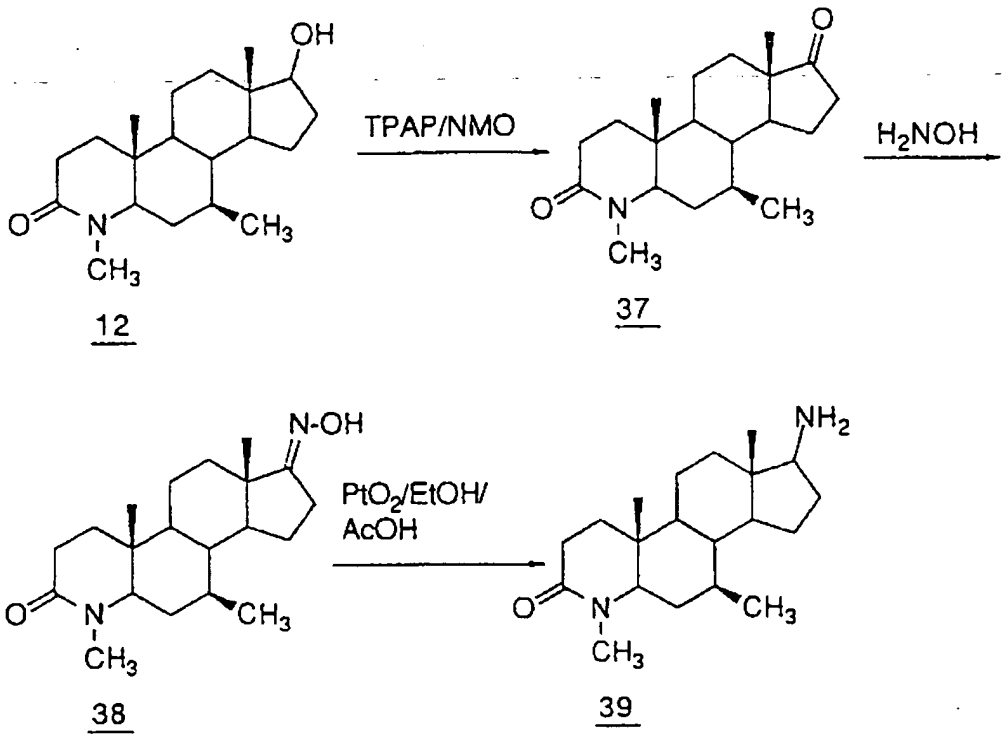
FLOWSHEET H



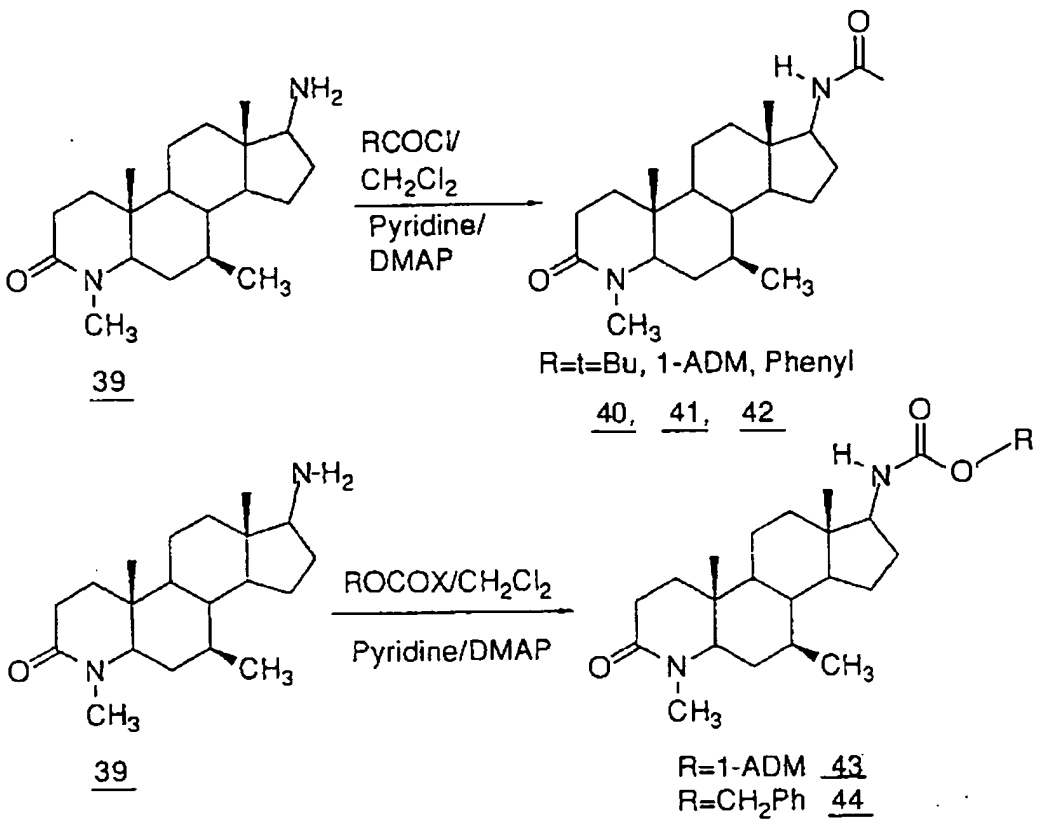
7-Keto-17-Carboxamide Series (illustrative)

The compound 34 is known in the art. This in can be oxidized with the chromium carbonyl reagent to yield the 5-en-7-one 35. The 5-double bond is catalytically reduced to yield the 7-one 36.

FLOWSHEET I



FLOWSHEET I (CONT'D)



7-Beta Methyl-17-Aza Series (illustrative)

This series can be prepared as illustrated in Flowsheet I starting with the 7-beta methyl-4-N-methyl-17-ol 12. This is oxidized to the 17-keto compound 37, by the use of tetrapropylammonium perruthenate (TPAP) and N-methylmorphiline-N-oxide (NMO) at room temperature. This is reacted in turn with hydroxylamine in ethanol, pyridine at 100°C to form the oxime 38, which is catalytically hydrogenated with platinum oxide in ethanol/acetic acid at room temperature to form the 17-amino 39.

The amine 39 can be reacted with a variety of acylating agents. Reaction with pivaloyl chloride in methylene chloride, pyridine, 4-dimethylamino pyridine (DMAP), yields 40, the "reverse finasteride"; reaction with 1-adamantane carbonyl chloride yields the 1-ADM 41; and reaction with benzoyl chloride yields the benzoyl derivative 42.

Reaction of the amine 39 with different chloroformates yields the corresponding urethanes. Reaction of 39 with 1-adamantyl fluoroformate in DMAP, pyridine and methylene chloride yields the urethane 43; reaction with e.g. benzyl chloroformate correspondingly yields 44.

Other acylating agents and chloroformates known in the art can be used to produce the corresponding acyl and urethane compounds.

The above 7-substituents can be introduced into all of the compounds delined for the 17-A group herein by appropriate analogous procedures.

Accordingly, the present invention is particularly concerned with providing a method of treating the hyperandrogenic conditions of androgenic alopecia, acne vulgaris, seborrhea, and female hirsutism, benign prostatic hyperplasia, prostatitis, the prevention and/or treatment of prostatic carcinoma, by oral, topical, or parenteral administration, of the novel compounds of the present invention.

The following examples are illustrative of representative preparative procedures.

PREPARATIVE EXAMPLE 1

Synthesis of 3-Acetoxy-Androst-5-en-17-ol (2)

To a solution of 100 mg. (0.303 mmol) of 3-acetoxy-androst-5-en-17-one, 1, in 3 ml EtOH at -10°C, was added 22.9 mg (0.606 mmol) of sodium borohydride with stirring. After the reaction mixture was stirred for one and 1/2 hours, the mixture was diluted with 10 ml water, the ethanol solvent removed under vacuum, and the residue extracted with ethyl acetate. The organic layer was washed with aqueous Na_2CO_3, brine, dried over sodium sulfate and concentrated to leave a residue of crude title compound 2. Proton NMR confirmed the assigned structure.

PREPARATIVE EXAMPLE 2

Synthesis of 3-Acetoxy-Androst-5-en-17-ol, 17-t-butyl-dimethylsilyl ether (3)

To a solution of the androstan-17-ol, 2. from Example 1, being 4.5 g (13.55 mmol) in 50 ml. dimethylformamide at 23°C was added 2.76 g (40-65 mmol) imidazole followed by 3.063 g (20.32 mmol) of t-butyldimethylsilyl chloride. The reaction mixture was stirred and a solid began to precipitate. Twenty additional ml of DMF were added was and the mixture further stirred overnight. The mixture was poured into 1 liter water, the solid filtered and washed with water. The solid was dissolved in ethylacetate, the organic layer washed with brine and dried over sodium sulfate, concentrated to yield the silyl protected 17-ol title compound 3. The proton NMR confirmed the assigned structure.

PREPARATIVE EXAMPLE 3

Synthesis of 3-Acetoxy-Androst-5-ene-7-one-17β-ol, 17-t-butyldimethylsilyl ether (4)

To a solution of the TBMS protected 17-ol 3 from Example 2, being 5.6 g (12.55 mmol) in 100 ml acetonitrile at 23°C was added 90% t-butyl hydrogen peroxide, 3.958g (43.92 mol), and 138 mg chromium hexacarbonyl. After refluxing the mixture under nitrogen for 24 hours, the reaction mixture was poured into one liter water, solid was filtered, the residue washed with 500 ml water and the residue dissolved in 350 ml methylene chloride. The organic layer was washed with brine, dried over sodium sulfate and concentrated to yield crude material. Thin layer chromatography (3:1 hexane/ethyl acetate on silica gel) showed the presence of starting material. The solid was purified by column chromatography over silica gel by elution with 7% ethyl acetate/hexane to yield the title compound 4. Proton NMR confirmed the assigned structure.

PREPARATIVE EXAMPLE 4

Synthesis of 3,7-Dihydroxy-7-methyl-Androst-5-en-17β-ol, 17-TBMS ether (5)

To a solution of the product 4 from Example 3, being 440 mg. (0.956 mmol) in dry tetrahydrofuran at 0°C was added dropwise methyl magnesium chloride over 5-10 minutes. The reaction mixture was then allowed to stir at room temperature for 24 hours, then poured into saturated aqueous ammonium chloride. The THF solvent was removed under vacuum and the aqueous phase extracted with ethyl acetate. The organic layer was washed with brine, dried, concentrated to yield crude product. Proton NMR confirmed the assigned structure of the title compound 5 which was used in the next step without further purification.

PREPARATIVE EXAMPLE 5

Synthesis of 7-methyl-Androst-4,6-dien-3-one-17β-ol, 17-t-butyldimethylsilyl ether (6)

The above Grignard product 5, 3.5g. (7.142 mmol) was dissolved in 50 ml toluene/50 ml. cyclohexanone and 20 ml of solvent distilled off under vacuum. To this was added 4.54 g. aluminum isopropoxide and the reaction mixture refluxed overnight for 15 hours. The mixture was cooled, diluted with ethyl acetate, washed with sodium potassium tartarate, brine, and the organic layer was concentrated under vacuum and the residue steam distilled. The residue was extracted with ethyl acetate, washed with brine, dried and purified by column chromatography on silica gel, eluting with 5% EtOAc/hexane to yield the title compound 6.

PREPARATIVE EXAMPLE 6

Synthesis of 7β-Methyl-Androst-5-en-3-one-17β-ol, t-Butyldimethylsilyl ether, (7)

To a solution of 370 mg of 6, from Example 5, in 5.5 ml ammonia, 1 ml THF, 1 ml. toluene, was added 50 mg. of metallic lithium in small pieces. After stirring the blue solution for 2 hours, a solution of 1,2-dibromethane in 2 ml THF was added. After stirring the solution at -78°C for 10 minutes, 250 mg of ammonium chloride was added and the mixture stirred for 10 minutes. The excess ammonia was removed by evaporation under a nitrogen steam. The reaction mixture was diluted with brine, extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to yield crude material 7 which was used as such in Example 7.

PREPARATIVE EXAMPLE 7

Synthesis of 7β-Methyl-Androst-4-en-3-on -17β-ol, t-Butyldimethylsilyl ether, (8)

To a solution of 7, from Example 6, being 432 mg in 4 ml THF was added 150 microliters DBU (1,8-diaza-bicyclo [5.4,0] undec-7-ene under nitrogen with stirring. The mixture was refluxed for 1.5 hours, then cooled, diluted with NH_4Cl solution. The solvent THF was removed under vacuum and the residue extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated under reduced pressure to yield crude material. The titled product 8 was purified by chromatography on silica gel using 10% EtOAc/ hexane as eluant.

PREPARATIVE EXAMPLE 8

Synthesis of 17β-(t-butyldimethylsilyloxy)-7β-methyl-5-oxo-A-nor3,5-secoandrostan-3-oic acid, (9)

To a solution of 884 mg of 8 in 15 ml. t-butyl alcohol at 80°C was added 248 mg sodium carbonate in 1.5 ml water followed by a dropwise addition over 15-20 minutes of a mixture of 2.273 g sodium periodate with 16.8 mg potassium permanganate in 8 ml. water. The reaction mixture was heated at 80°C for 2 hours, cooled, filtered, the residue washed with water, and then the extract L-concentrated under vaccum. The extract was acidified with aqueous HCl, extracted with ethyl acetate and the organic layer washed with aqueous $NaHSO_3$, brine, dried and concentrated to yield crude 9. The proton NMR confirmed the assigned structure.

An essential feature of the invention is that;

A is $-(CHR^1)_n-XR^4$;

n is 1-10;

X is -O- or $-S(O)_p-$;

wherein p is zero, 1 or 2; and

R^1 can be the same or different when n is greater than 1 and is -H, aryl, or $-C_{1-3}$alkyl unsubstituted or substituted with aryl;

R is -H, methyl or ethyl;

R^4 1) is $-C_{1-20}$ alkyl, unsubstituted or substituted with one or more of:

a) -OH,
b) halo,
c) $-C_{1-8}$ alkoxy,
d) $-C_{1-6}$ alkenyl,
e) $-CONR^5R^5$, wherein R^5 is independently

i) -H,
ii) $-C_{1-8}$ alkyl unsubstituted or substituted with one or more of R^7, aryl or heterocycle, the aryl being unsubstituted or substituted with one or more of R^7 or R^9,
iii) aryl unsubstituted or substituted with one or more of R^7 or R^9, or
iv) heterocycle, unsubstituted or substituted with one or more of R^7 or R^9,

f) $-COOR^6$, wherein R^6 is

i) -H,
ii) $-C_{1-8}$ alkyl unsubstituted or substituted with one or more of R^7 or aryl, the aryl being unsubstituted or

substituted with one or more of R^7 or R^9, or
iii) aryl, unsubstituted or substituted with one or more of R^7 or R^9,

g) $-S(O)_p-R^5$, wherein p is defined above,
h) $-N(R^5)_2$,
i) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9,
j) heterocycle, unsubstituted or substituted with one or more of R^7 or R^9,
k) $-C_{3-10}$ cycloalkyl, such as cyclohexyl,norbornyl, or adamantyl, unsubstituted or substituted with one or more of R^7 or R^9, or

1) $-CONR^8-CO-NHR^8$, wherein R^8 is -H, $-C_{1-8}$ alkyl, benzyl or cyclohexyl; or
2) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9, or
3) heterocycle or $-C_{3-10}$ cycloalkyl, either of which is unsubstituted or substituted with one or more of R^7 or R^9;

R^7 is

1) -CN,
2) $-C_{1-3}$ alkoxy,
3) -CN,
4) $-COOR^6$
5) $-C_{1-8}$alkyl-$COOR^6$
6) $-NO_2$, or
7) -halo; and
8) amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino;

R^9 is 1) $-C_{1-8}$ alkyl, unsubstituted or substituted with one or more of aryl or R^7,
2) -CO-A, $-C_{1-8}$ alkyl-CO-A, -NHCO-A, or $S(O)_p$-A, wherein p is defined above and A is

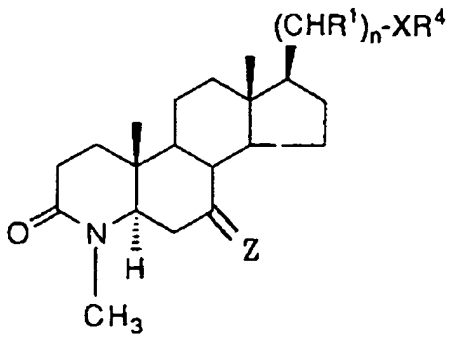
a) -H,
b) $-C_{1-8}$ alkyl, unsubstituted or substituted with one or more of

i) $-R^7$, or
ii) aryl, unsubstituted or substituted with one or more of R^7, or

c) aryl, unsubstituted or substituted with one or more of R^7,

3) -NHCO-heterocycle,
4) $-N(R^{10})_2$ or $-CON(R^{10})_2$ wherein R^{10} is independently -H, heterocycle, or -A,
5) $-NHCO-(CH_2)_q-CO-Q$, wherein q is 1-4, and Q is $-N(R^{10})_2$ or $-OR^{10}$.

A preferred embodiment of this invention is represented by compounds of general structural formula VII:



VII

wherein R^4 is -C_{1-20} alkyl, unsubstituted or substituted with one or more of -OH, halo, -C_{1-8}alkoxy, -C_{1-6}alkenyl, -$S(O)_p$-R^5, -$N(R^5)_2$, aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9, heterocycle unsubstituted or substituted with one or more of R^7 or R^9, or -C_{3-10} cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9, and X, R^1, n, p, R^5, R^7 and R^9 are defined as in general structural formula I.

Another preferred embodiment of this invention is represented by compounds of general structural formula VII wherein R^4 is -C_{1-20} alkyl substituted with -$CONR^5R^5$, -$COOR^6$ or -$CONR^8CONHR^8$, and X, R^1, n, R^5, R^6 and R^8 are defined as in general structural formula I.

Another preferred embodiment of this invention is represented by compounds of formula VII wherein R^4 is aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9; heterocycle unsubstituted or substituted with one or more of R^7 or R^9; or -C_{3-10} cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9; and X, R^1, n, R^7 and R^9 are defined as in general structural formula I.

Also included within the scope of this invention are pharmaceutically acceptable salts where a basic or acidic group is present in a compound of formula I, such as on the substituted alkyl, cycloalkyl, aryl or heterocyclic moiety. When an acidic substituent is present, i.e. -COOH, there can be formed the ammonium, sodium, potassium, calcium salt, and the like, for use as the dosage form.

Where a basic group is present, i.e. amino, acidic salts, i.e. hydrochloride, hydrobromide, acetate, pamoate, and the like, can be used as the dosage form.

The compounds of the present invention, may have asymmetric centers and occur as racemates, racemic mixtures and as individual diastereomers, with all isomeric forms being included in the present invention.

When any variable (e.g., aryl, heterocycle, R^1, R^2, n, X, etc.) occurs more than one time in any constituent or general structural formula its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms (Me is methyl, Et is ethyl, Pr is propyl, Bu is butyl); "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Cycloalkyl" is intended to include saturated mono-, bi- and tricyclic ring groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl (Cyh), cycloheptyl, norbornanyl and adamantyl. "Alkenyl" is intended to include hydrocarbon groups of either a straight or branched configuration with one or more carbon-carbon double bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, and the like. "Halo", as used herein, means fluoro, chloro, bromo and iodo.

As used herein, with exceptions as noted, "aryl" is intended to mean phenyl (Ph) or naphthyl.

The term heterocycle or heterocyclic, as used herein except where noted, represents a stable 5- to 7-membered monocyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thia-

zolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazoyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl. Morpholino is the same as morpholinyl. Preferred heterocycles are piperidinyl, 2-oxopyrrolodinyl, pyrrolyl, pyrazolyl, imidazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, morpholinyl, thiazolyl, isothiazolyl, quinuclidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazoyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, thienyl, and benzothienyl.

As used herein, "heteroaryl" represents a stable 5- to 7-membered monocyclic unsaturated heterocyclic ring, which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized.

Further abbreviations that may appear herein are defined as follows:

DCC	N,N'-dicyclohexylcarbodiimide
DIC	1,3-diisopropylcarbodiimide
DEAD	diethyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	N, N-dimethylformamide
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
Ph_3P	triphenylphosphine
m.p (or mp)	melting point
THF	tetrahydrofuran
m.w. (or mw)	molecular weight

PREPARATIVE EXAMPLE 9

Synthesis of 4,7β-Dimethyl-4-aza-Androst-5-en-3-one-17β-ol, t-butyldimethylsilyl ether

To a solution of the product of preparative Example 8 (17β-(t-butyldimethylsilyloxy)-7β-methyl-5-oxo-A-nor-3,5-secoandrostan-3-oic acid), 840 mg in 5 ml ethylene glycol was added 1.5 g sodium acetate and 737 mg. methylamine hydrochloride. After stirring the reaction mixture 4 hours at 180°C, the mixture was cooled, diluted with water, extracted with ethyl acetate, dried and concentrated to afford crude title compound Proton NMR confirmed the assigned structure.

PREPARATIVE EXAMPLE 10

Synthesis of 4,7β-Dimethyl-4-aza-Androst-5-en-3-one-17β-ol

To a solution of 700 mg of the product from preparative Example 9 in 20 ml of acetonitrile at 0°C was added 500 microliters. aqueous HF. After stirring the reaction mixture for one hour, the HF was neutralized with aqueous sodium carbonate, diluted with water, acetonitrile removed under vacuum, and the residue extracted with ethyl acetate. The organic layer was dried, concentrated to give crude title compound which was further purified by preparative chromatography on silica gel using 3:1 chloroform/acetone.

PREPARATIVE EXAMPLE 11

Synthesis of 4,7β-dimethyl-4-aza-androstan-3-one-17β-ol

To a solution of the product from preparative Example 10, being 350 mg in 10 ml acetic acid was added 100 mg platinum dioxide and the resulting mixture was evacuated and flushed with hydrogen. The reaction was shaken overnight at room temperature under 40 Psig hydrogen pressure. The solution was filtered concentrated. The residue was worked up with ethyl acetate, the organic layer was then concentrated under vacuum, diluted with ethyl acetate, washed with aqueous $NaHCO_3$, brine, dried, concentrated to yield the title compound Mass Spec: 320 (M+1).

PREPARATIVE EXAMPLE 12

Synthesis of 17β-pivaloyloxy-4,7β-Dimethyl-4-Aza-Androstan-3-one

To a solution of the product from preparative Example 11, being 60.2 mg in 4 ml methylene chloride and 200 ml

pyridine was added 15 mg DMAP (4-dimethylaminopyridine) followed by 68.66 mg pivaloyl chloride, i.e., trimethyl acetyl chloride. After stirring for 24 hours, the reaction mixture was diluted with ethyl acetate, washed with water, then aqueous sodium carbonate and brine. The organic layer was dried, concentrated to a residue, which was purified by preparative chromatography on silica gel using 3:1 chloroform/acetone as eluant to yield pure title compound Proton NMR confirmed the assigned structure.

PREPARATIVE EXAMPLE 13

Synthesis of 17β-(t-Butylaminocarbonyloxy)-4,7-dimethyl-5α-4-aza-Androstan-3-one

To a solution of the title compound of preparative Example 12, 51 mg in 4 ml methylene chloride was added DBU (200 microliters) followed by 63.65 mg. t-butylisocyanate. After stirring the mixture for 48 hours at room temperature, the reaction mixture was diluted with ethyl acetate, the organic layer washed with water, brine, dried and concentrated to a residue which was purified by preparative chromatography over silica gel using 3:1 $CHCl_3$/acetone to yield pure title compound.

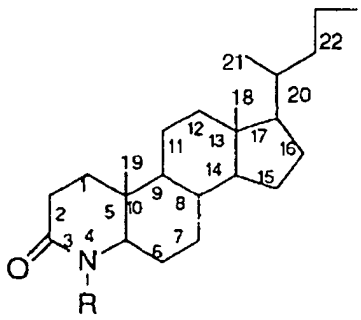
PREPARATIVE EXAMPLE 14

Synthesis of 17β-Methoxycarbonyl-4-methyl-4-aza-androst-5-en-3,7-dione

Following the analogous oxidation procedure of preparative Example 3, 17β-methoxycarbonyl-4-methyl-4-aza-5α-androstan-3-one, known in the art, was analogously treated to yield the title compound.

The following Table 5 lists the unique proton NMR values (400 MHz in $CDCl_3$) for several of the above-described compounds. The data are reported as: s = singlet, d = doublet, m = multiplet, J = coupling constant. The absorption values are given del (d) units and are illustrated for the C-18, C-19 and methyl protons and protons associated with unique portions of the molecule.

The numbering of the steroid is given by the following structure;



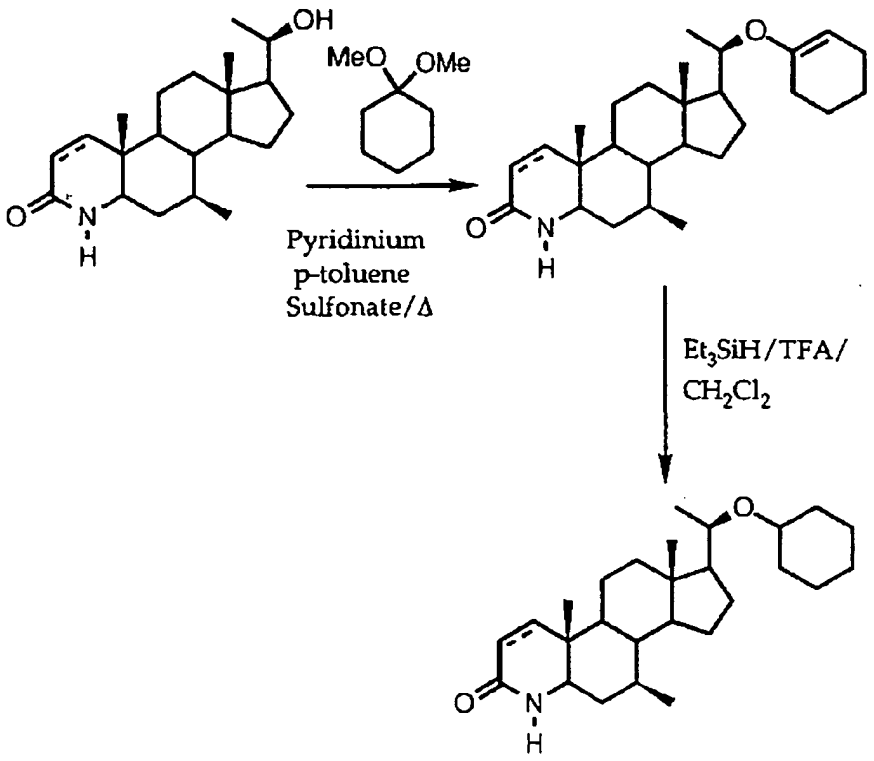
NMR DATA

Title compound of Preparative Example No.	C-18 CH_3	C-19 CH_3	Others
9	0.72	1.02	7 Me, 3H, d, 1.04 J=6.5 6H, 1H, d, 4.78 J=3
10	0.78	1.02	7 Me, 3H, d, 1.06, J=6.5 6H, 1H, d, 4.79, J=3
11	0.74	0.86	7 Me, 3H, d, 1.02, J=6.5 5H, 1H, dd, 3.10 J=4.5 J=13.5
12	0.82	0.85	N-CH_3, 3H, S, 2.90 C-5, 1H, dd, 3.01 J=12.6 J= 3.7 C-7ß-CH_3, 3H, d, 1.02, J= 6.5
13	0.76	0.82	N-CH_3, 3H, S, 2.89 C-5, 1H, dd, 3.01 J= 3.7 J=12.6

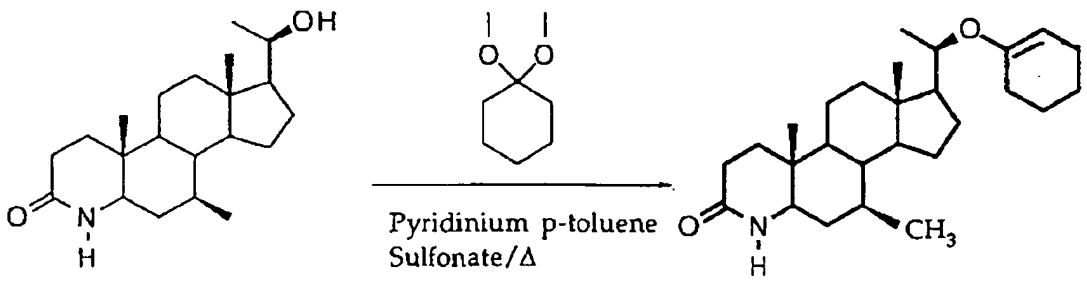
C-7β-CH_3, 3H; d,
1.02, J= 6.5

Another preferred embodiment of this invention is a series of compounds characterized in having ether moieties at the 17 position, and which can be synthesized according to the following flowsheet:

Flowsheet XXXIII



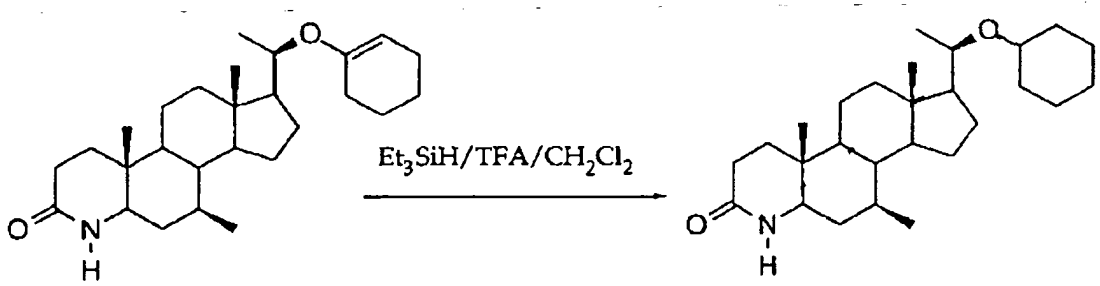
EXAMPLE 15



To a solution of Azasteroid (250mg) in dimethoxycyclohexane (10ml) was added pyridinum p-toluenesulfonate and

reaction mixture was heated at 140° for 2hrs. The temperature of reaction was increased and dimethoxycyclohexane was removed slowly by distillation over 4hrs. Finally all the dimethoxycyclohexane was distilled off and residue taken in ethyl acetate, washed with aqueous sodium bicarbonate, brine, dried and concentrated to give 2. MS calculated for $C_{27}H_{43}NO_2$, 413.65. Observed 413 (EI).

EXAMPLE 16



To a solution of Enol Ether (150 mg) in CH2C12 (2ml) was added triethylsilane (418.6 mg, 10 eq.) followed by slow dropwise addition of TFA (2.07g). After stirring the reaction for overnight at room temperature, the reaction mixture was diluted with CH2C12, washed with aq. $NaHCO_3$, brine, dried and concentrated. The residue was purified by prep. tlc over sliica gel using 30% acetone/ CH2C12 as solvent. MS calculated for $C_{27}H_{45}NO_2$, 415.66. Observed 415(EI).

In this specification , Rf values cited were carried out on standard thin layer chromatographic Silica gel plates. The elution solvent system used is given in the parentheses following the Rf value.

The mass spectral values cited are given as FAB, i.e., fast atom bombardment, and are reported as (M+1) molecular ion peaks, being the molecular weight plus one atomic mass unit. The electron impact (EI) mass spectrum values cited are reported as molecular ion peaks and are indicated in parentheses, either being (M) or (M+2), the molecular weight, MW, or the MW plus two atomic units.

The nuclear magnetic resonance data was taken at 400 MHz in $CDCl_3$ and is tabulated for representative unique proton values. The coupling constant J is given in Hertz, Hz.

The present invention has the objective of providing suitable topical, oral and parenteral pharmaceutical formulations for use in the novel methods of treatment of the present invention.

The compositions containing the compounds of the present invention as the active ingredient for use in the treatment of e.g., benign prostatic hypertrophy, prostatitis, and treatment and prevention of prostatic carcinoma, hyperandrogenic conditions, can be administered in a wide variety of therapeutic dosage forms in conventional vehicles for systemic administration, as, for example, by oral administration in the form of tablets, capsules, solutions, or suspensions, or by injection. The daily dosage of the products may be varied over a wide range varying from 0.5 to 1,000 mg per adult human/per day. The compositions are preferably provided in the form of scored tablets containing 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, and 50.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.002 mg. to about 50 mg./kg. of body weight per day. Preferably the range is from about 0.01 mg. to 7 mg./kgs. of body weight per day. These dosages are well below the toxic dose of the product. For the treatment of androgenic alopecia, acne vulgaris, seborrhea, female hirsutism, the compounds of the present invention are administered in a pharmaceutical composition comprising the active compound in combination with a pharmacologically acceptable carrier adapted for topical, oral or parenteral administration.

These topical pharmaceutical compositions may be in the form of a cream, ointment, gel or aerosol formulation adapted for application to the skin. These topical pharmaceutical compositions containing the compounds of the present invention ordinarily include about 0.1% to 15%, preferably about 5%, of the active compound, in admixture with about 95% of vehicle.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixers, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as a 5 α-reductase agent.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of

factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug.

Oral dosages of the present invention, when used for the indicated effects, will range between about Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittant throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, zanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropyl- methacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

BIOLOGICAL ASSAYS

Preparation of Human prostatic and scalp 5a-reductases.

Samples of human tissue were pulverized using a freezer mill and homogenized in 40 mM potassium phosphate, pH 6.5, 5 mM magnesium sulfate, 25 mM potassium chloride, 1 mM phenylmethylsulfonyl fluoride, 1 mM dithiothreitol (DTT) containing 0.25 M sucrose using a Potter-Elvehjem homogenizer. A crude nuclear pellet was prepared by centrifugation of the homogenate at 1,500xg for 15 min. The crude nuclear pellet was washed two times and resuspended in two volumes of buffer. Glycerol was added to the resuspended pellet to a final concentration of 20%. The enzyme suspension was frozen in aliquots at -80°C. The prostatic and scalp reductases were stable for at least 4 months when stored under these conditions.

5α-reductase assay.

The reaction mixture contained in a final volume of 100 µl is: 40 mM buffer (human scalp, potassium phosphate, pH 6.5; human prostatic 5α-reductase, sodium citrate, pH 5.5), 0.3-10 µM ^{14}C-T (or ^{3}H-T), 1 mM DTT, and 500 µM NADPH. Typically, the assay was initiated by the addition of 50-100 µg prostatic homogenate or 75-200 µg scalp homogenate and incubated at 37°C. After 10-50 min the reaction was quenched by extraction with 250 µl of a mixture of 70% cyclohexane: 30% ethyl acetate containing 10 µg each DHT and T. The aqueous and organic layers were separated by centrifugation at 14,000 rpm in an Eppendorf microfuge. The organic layer was subjected to normal phase

HPLC (10 cm Whatman partisil 5 silica column equilibrated in 1 ml/min 70 % cyclohexane: 30 % ethyl acetate; retention times DHT, 6.8-7.2 min; androstanediol, 7.6-8.0; T, 9.1-9.7 min). The HPLC system consisted of a Waters Model 680 Gradient System equipped with a Hitachi Model 655A autosampler, Applied Biosystems Model 757 variable UV detector, and a Radiomatic Model A120 radio-activity analyzer. The conversion of T to DHT was monitored using the radioactivity flow detector by mixing the HPLC effluent with one volume of Flo Scint 1 (Radiomatic). Under the conditions described, the production of DHT was linear for at least 25 min. The only steroids observed with the human prostate and scalp preparations were T, DHT and androstanediol.

Stumptail macaque protocol

The following protocol is utilized with the stumptail macaque monkey to demonstrate the effect of compounds of the present invention for promoting hair growth.

Twenty-one male stumptail macaque monkeys of species *Macaca speciosa* are assigned to vehicle control and drug treatment groups on the basis of baseline hair weight data. This assignment procedure is necessary to insure that the average baseline hair growth for each control and experimental group is comparable. The control and drug treatment groups are as follows:

1. Topical 50:30:20 vehicle (N= 6)
2. Oral 5α-reductase and topical 50:30:20 vehicle (N = 5)
3. Oral placebo (N = 5)
4. 5α-reductase in vehicle (N = 5)

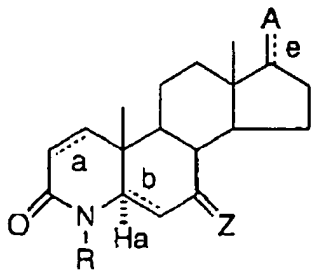
The vehicle consists of 50% propylene glycol, 30% ethanol and 20% water. A 100 mM concentration of topical 5α-reductase is formulated in this vehicle. The same 5α-reductase is administered as an oral dose of 0.5mg per monkey. Immediately prior to the dosing phase of the study, hair is removed from a 1 inch square area (identified by four tatoos) in the center of the balding scalp. This hair collection is the baseline hair growth determination prior to the beginning of treatment.

Approximatly 250µL of vehicle and 5α-reductase in vehicle is prepared and topically administered to the tatooed area of the scelp. The selected 5α-reductase and placebo is ingested by the monekys at the same time as the topical doses are administered. The monkeys are dosed once per day, seven days per week for twenty weeks.

At four week intervals throughout the dosing phase of the study, each monkey is shaved and the hair is collected and weighed. The body weight data (at baseline and during assay) is analyzed by the nonparametric Wilcoxon rank-sum test. Differences are significant at $p < 0.05$. Hair weight data at each week collection for vehicle, placebo and treatment groups are expressed as the change from baseline. Statistical analysis is performed on the rank of the data to show overall differences among groups at each four week collection.

Claims

1. A compound of the formula:

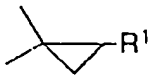


wherein

R is selected from hydrogen, methyl or ethyl; the dashed lines-a, b, e indicate double bonds which can be present, providing that if b double bond is present, then the 5α hydrogen, Ha, is not present;

Z is selected from

1) oxo,
2) a-hydrogen and a β-substituent selected from C_1-C_4 alkyl, C_2-C_4 alkenyl, -CH_2COOH, hydroxy, carboxy, $COOC_1$-C_4 alkyl esters; $OCONR^1R^2$, where R^1 and R^2 are independently H, C_1-C_4 alkyl, phenyl, benzyl, and where R^1 and R^2 together with the nitrogen can form a 5-6 membered saturated heterocyclic ring, optionally with one other heteroatom; OC_1-C_4 alkyl, OC_3-C_6 cycloalkyl, -$OCOCH_3$, halo, halo C_1-C_2 alkyl, or trifluoromethyl, C_3-C_6 cycloalkyl;
3)= CH-R^1 where R^1 is H, C_1-C_4 alkyl;
4)Spiro



where R^1 is H, C_1-C_4 alkyl; and

A is -$(CHR^1)_n$-XR^4 ;
n is 1-10;
X is -O- or -$S(O)_p$-, wherein p is zero, 1 or 2; and
R^1 can be the same or different when n is greater than 1 and is -H, aryl, or -C_{1-3}alkyl unsubstituted or substituted with C_6-C_{10} aryl;
R is -H, methyl or ethyl;
R^4 is 1) hydrogen or -C_{1-20} alkyl, unsubstituted or substituted with one or more of:

a) -OH,
b) halo,
c) -C_{1-8} alkoxy,
d) -C_{1-6} alkenyl,
e) -$CONR^5R^5$, wherein R^5 is independently

i) -H,
ii) -C_{1-8} alkyl unsubstituted or substituted with one or more of R^7, aryl or heterocyclic, defined below, the aryl being unsubstituted or substituted one or more of R^7 or R^9,
iii) aryl unsubstituted or substituted with one or more of R^7 or R^9, or
iv) heterocyclic, defined below, unsubstituted or substituted with one or more of R^7 or R^9,

f) -$COOR^6$, wherein R^6 is

i) -H,
ii) -C_{1-8} alkyl unsubstituted or substituted with one or more of R^7 or aryl, the aryl being unsubstituted or substituted with one or more of R^7 or R^9, or
iii) aryl, unsubstituted or substituted with one or more of R^7 or R^9,

g) -$S(O)_p$-R^5, wherein p is defined above,
h) -$N(R^5)_2$,
i) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9,
j) heterocycle, unsubstituted or substituted with one or more of R^7 or R^9,
k) -C_{3-10} cycloalkyl, such as cyclohexyl,norbornyl, or adamantyl, unsubstituted or substituted with one or more of R^7 or R^9, or

1) -$CONR^8$-CO-NHR^8, wherein R^8 is -H, -C_{1-8} alkyl, benzyl or cyclohexyl; or
2) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9, or
3) heterocycle or -C_{3-10} cycloalkyl, either of which is unsubstituted or substituted with one or more of R^7 or R^9;

R^7 is

1) -OH
2) -C_{1-3} alkoxy,
3) -CN,
4) -$COOR^6$
5) -C_{1-8} alkyl-$COOR^6$
6) -NO_2, or
7)-halo; and
8) amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino;

R^9 is

1) -C_{1-8} alkyl, unsubstituted or substituted with one or more of aryl or R^7,
2) -CO-A, -C_{1-8} alkyl-CO-A, -NHCO-A, or -$S(O)_p$-A,
wherein p is defined above and A is

a) -H,
b) -C_{1-8} alkyl, unsubstituted or substituted with one or more of

i) -R^7, or
ii) aryl, unsubstituted or substituted with one or more of R^7, or

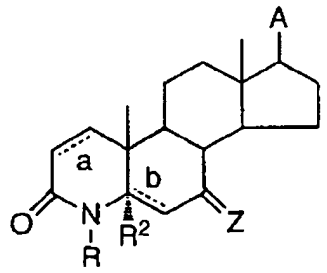
c) aryl, unsubstituted or substituted with one or more of R^7,

3) -NHCO-heterocycle,
4) -$N(R^{10})_2$ or -$CON(R^{10})_2$ wherein R^{10} is independently -H, heterocycle, or -A,
5) -NHCO-$(CH_2)_q$-CO-Q, wherein q is 1-4, and Q is -$N(R^{10})_2$ or -OR^{10};

the term heterocycle or heterocyclic, as used herein except where noted, represents a stable 5- to *7-membered* monocyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring, the heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure,

and pharmaceutically acceptable salts thereof.

2. The compound of Claim I of the formula



wherein: Z is defined in Claim 1;
wherein a and b are both single bonds and R^2 is hydrogen, or a is a double bond, b is a single bond and R^2 is hydrogen, or a is a single bond, b is a double bond and R^2 is absent;

A is -$(CHR^1)_n$-XR^4;
n is 1-10;
X is -O- or -$S(O)_p$-,

wherein p is zero, 1 or 2; and

R^1 is -H, aryl, or -C_{1-3}alkyl unsubstituted or substituted with C_{6-10} aryl;

R is -H, methyl or ethyl;

R^4 is

1) -C_{1-20} alkyl, unsubstituted or substituted with one or more of:

a) -OH,
b) halo,
c) -C_{1-8} alkoxy,
d) -C_{1-6} alkenyl,
e) -$CONR^5R^5$, wherein R^5 is independently

i) -H,
ii) -C_{1-8} alkyl unsubstituted or substituted with one or more of R^7, aryl or heterocycle, the aryl being unsubstituted or substituted with one or more of R^7 or R^9,
iii) aryl unsubstituted or substituted with one or more of R^7 or R^9, or
iv) heterocycle, unsubstituted or substituted with one or more of R^7 or R^9,

f) -$COOR^6$, wherein R^6 is

i) -H,
ii) -C_{1-8} alkyl unsubstituted or substituted with one or more of
R^7 or aryl, the aryl being unsubstituted or substituted with one or more of R^7 or R^9, or
iii) aryl, unsubstituted or substituted with one or more of R^7 or R^9,

g) -$S(O)_p$-R^5, wherein p is defined above,
h) -$N(R^5)_2$,
i) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9,
j) heterocycle, unsubstituted or substituted with one or more of R^7 or R^9,
k) C_{3-10} cycloalkyl, such as cyclohexyl,norbornyl, or adamantyl, unsubstituted or substituted with one or more of R^7 or R^9, or

1) -$CONR^8$-CO-NHR^8, wherein R^8 is -H,-C_{1-8} alkyl, benzyl or cyclohexyl; or
2) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9, or
3) heterocycle or -C_{3-10} cycloalkyl, either of which is unsubstituted or substituted with one or more of R^7 or R^9;

R^7 is

1) -OH,
2) -C_{1-3} alkoxy,
3) -CN,
4) -$COOR^6$
5) -C_{1-8}alkyl-$COOR^6$
6) -NO_2, or
7) -halo; and
8) amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino;

R^9 is

1) -C_{1-8} alkyl, unsubstituted or substituted with one or more of aryl or R^7,
2) -CO-A, -C_{1-8} alkyl-CO-A, -NHCO-A, or -$S(O)_p$-A, wherein p is defined above and A is

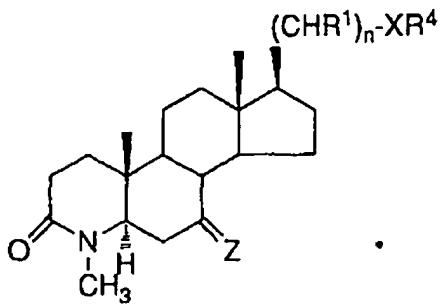
a) -H,
b) -C_{1-8} alkyl, unsubstituted or substituted with one or more of

i) -R^7, or
ii) aryl, unsubstituted or substituted with one or more of R^7, or

c) aryl, unsubstituted or substituted with one or more of R^7,

3) -NHCO-heterocycle,
4) $-N(R^{10})_2$ or $-CON(R^{10})_2$ wherein R^{10} is independently -H, heterocycle, or -A,
5) $NHCO-(CH_2)_q-CO-Q$, wherein q is 1-4,and Q is $-N(R^{10})_2$ or $-OR^{10}$.

3. The compound of Claim 2 having structural formula:



4. The compound of Claim 3 wherein R^4 is $-C_{1\text{-}20}$ alkyl, unsubstituted or substituted with one or more of -OH, halo, $-C_{1\text{-}6}$aloxy, $-C_{1\text{-}6}$alkenyl, $-S(O)_p-R^5$, $-N(R^5)_2$, aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9, heterocycle unsubstituted or substituted with one or more of R^7 or R^9, or $-C_{3\text{-}10}$ cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9.

5. The compound of Claim 3 wherein R^4 is $-C_{1\text{-}20}$ alkyl substituted with $-CONR^5R^5$, $-COOR^6$ or $-CONR^8CONHR^8$.

6. The compound of Claim 3 wherein R^4 is aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9; heterocycle unsubstituted or substituted with one or more of R^7 or R^9; or $-C_{3\text{-}10}$ cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9.

7. The use of a compound of Claim 1 for the manufacture of a medicament for treating the hyperandrogenic conditions of acne, androgenic alopecia, male pattern baldness, female hirsutism, benign prostatic hyperplasia, prostatitis, treatment and prevention of prostatic cancer.

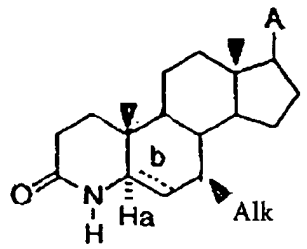
8. The use as claimed in Claim 7 wherein said compound is a 5α-reductase 1 inhibitor.

9. The use as claimed in Claim 7 wherein said compound is a 5α-reductase 2 inhibitor.

10. The use as claimed in Claim 7 wherein said compound is a dual inhibitor for both 5α-reductase 1 and 2.

11. A pharmaceutical composition comprising a therapeutically effective amount of the compound of Claim 1 in a pharmaceutically acceptable vehicle therefor.

12. A process for the synthesis of a compound of the formula



General Formula I

wherein

R is selected from hydrogen, methyl or ethyl; the dashed lines-a, b, e indicate double bonds which can be present, providing that if double bond b is present then the 5α hydrogen, Ha, is not present; where Alk is C_1-C_4 alkyl, C_2-C_4 alkenyl, $-CH_2COOH$, hydroxy, carboxy, $COOC_1$-C_4 alkyl esters;

A is $-(CHR^1)_n-XR^4$;

n is 1-10;

X is -O- or $-S(O)_p-$,

wherein p is zero, 1 or 2; and

R^1 can be the same or different when n is greater than 1 and is -H, aryl, or $-C_{1-3}$alkyl unsubstituted or substituted with C_6-C_{10} aryl;

R is -H, methyl or ethyl;

R^4 is 1) hydrogen or $-C_{1-20}$ alkyl, unsubstituted or substituted with one or more of:

a) -OH,
b) halo,
c) $-C_{1-8}$ alkoxy,
d) $-C_{1-6}$ alkenyl,
e) $-CONR^5R^5$, wherein R^5 is independently

i) -H,
ii) $-C_{1-8}$ alkyl unsubstituted or substituted with one or more of R^7, aryl or heterocyclic, defined below, the aryl being unsubstituted or substituted with one or more of R^7 or R^9,
iii) aryl unsubstituted or substituted with one or more of R^7 or R^9, or
iv) heterocyclic, defined below, unsubstituted or substituted with one or more of R^7 or R^9,

f) $-COOR^6$, wherein R^6 is

i) -H,
ii) $-C_{1-8}$ alkyl unsubstituted or substituted with one or more of R^7 or aryl, the aryl being unsubstituted or substituted with one or more of R^7 or R^9, or
iii) aryl, unsubstituted or substituted with one or more of R^7 or R^9,

g) $-S(O)_p-R^5$, wherein p is defined above,
h) $-N(R^5)_2$,
i) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9,
j) heterocyclic, unsubstituted or substituted with one or more of R^7 or R^9,
k) $-C_{3-10}$ cycloalkyl, unsubstituted or substituted with one or more of R^7 or R^9, or

1)$-CONR^8-CO-NHR^8$, wherein R^8 is -H, $-C_{1-8}$ alkyl, benzyl or cyclohexyl; or
2) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9, or

3) heterocycle or -C_{3-10} cycloalkyl, either of which is unsubstituted or substituted with one or more of R^7 or R^9;

R^7 is 1) -OH,

2) -C_{1-3} alkoxy,
3) -CN,
4) -$COOR^6$
5) -C_{1-8}alkyl-$COOR^6$
6) -NO_2, or
7) -halo; and
8) amino, mono C_1-C_4 alkylamino, di C_1-C_4 alkylamino;

R^9 is

1) -C_{1-8} alkyl, unsubstituted or substituted with one or more of aryl or R^7,
2) -CO-A, -C_{1-8} alkyl-CO-A, -NHCO-A, or -$S(O)_p$-A, wherein p is defined above and A is

a) -H,
b) -C_{1-8} alkyl, unsubstituted or substituted with one or more of

i) -R^7, or
ii) aryl, unsubstituted or substituted with one or more of R^7, or

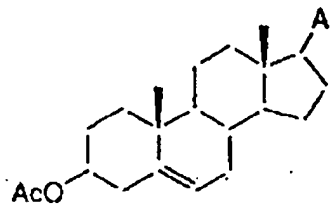
c) aryl, unsubstituted or substituted with one or more of R^7,

3) -NHCO-heterocyclic,
4) -$N(R^{10})_2$ or -$CON(R^{10})_2$ wherein R^{10} is independently -H, heterocyclic, or -A,
5) -NHCO-$(CH_2)_q$-CO-Q, wherein q is 1-4, and Q is -$N(R^{10})_2$ or -OR^{10};

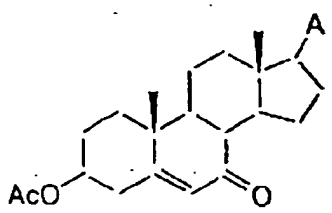
the term heterocycle or heterocyclic, as used herein except where noted, represents a stable 5- to *7-membered* monocyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring, the heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure,

which process comprises the steps of

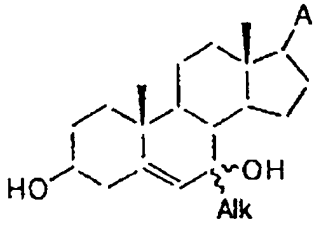
(a) oxidizing a compound of the formula



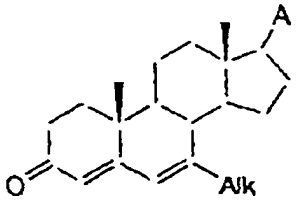
to produce the corresponding ketone of the formula



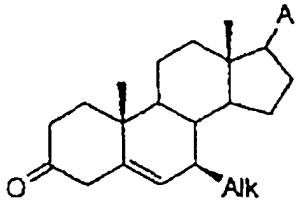
(b) alkylating the product of (a) to produce the corresponding alkylhydroxy adduct of the formula



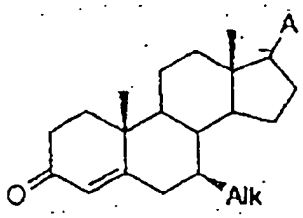
(c) oxidizing the product of (b) to produce a diene of the formula



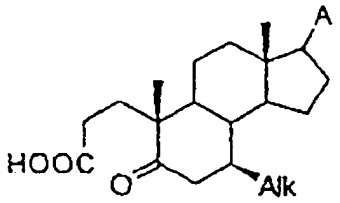
(d) reducing the product of (c) to produce a compound of the formula



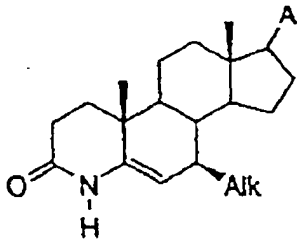
(e) isomerizing the product of (d) to produce the 4-ene of the formula



(f) cleaving the A ring in the product of (e) to produce a seco acid of the formula



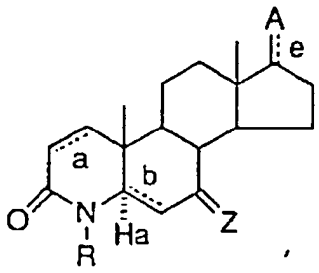
and
(g) closing the ring the product to produce a 4-alkyl-4-aza-androst-5- ene compound of the formula



followed by optional selective reduction of the 5-double bond.

Patentansprüche

1. Eine Verbindung der Formel:



worin

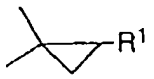
R ausgewählt ist aus Wasserstoff, Methyl oder Ethyl, die gestrichelten Linien a, b, e Doppelbindungen bedeuten, die vorliegend können, mit der Maßgabe, daß, wenn die b-Doppelbindung vorliegt, das 5α-Wasserstoff, Ha, dann nicht vorhanden ist,

Z ausgewählt ist aus

1) Oxo,

2) einem α-Wasserstoff und einem β-Substituenten, der ausgewählt ist aus C_1-C_4-Alkyl, C_2-C_4-Alkenyl, -CH_2COOH, Hydroxy, Carboxy, COO-C_1-C_4-Alkylestern, OCONR^{1}R^2, worin R^1 und R^2 unabhängig voneinander H, C_1-C_4-Alkyl, Phenyl, Benzyl sind, und worin R^1 und R^2 zusammen mit dem Stickstoff einen 5-6gliedrigen gesättigten heterocyclischen Ring, gegebenenfalls mit einem anderen Heteroatom, bilden

können, OC_1-C_4-Alkyl, OC_3-C_6-Cycloalkyl, $-OCOCH_3$, Halogen, Halogen-C_1-C_2-alkyl oder Trifluormethyl, C_3-C_6-Cycloalkyl,
3) $=CH-R^1$, worin R^1 H, C_1-C_4-Alkyl ist,
4) Spiro



worin R^1 H, C_1-C_4-Alkyl ist, und

A $-(CHR^1)_n-XR^4$ ist,
n 1-10 ist,
X -O- oder $-S(O)_p-$ ist, worin p null, 1 oder 2 ist, und
R^1, wenn n größer als 1 ist, gleich oder verschieden sein kann, und -H; Aryl oder $-C_{1-3}$-Alkyl, unsubstituiert oder substituiert mit C_6-C_{10}-Aryl, ist,
R -H, Methyl oder Ethyl ist,
R^4 ist

1) Wasserstoff oder $-C_{1-20}$-Alkyl, das unsubstituiert oder substituiert ist mit einem oder mehreren der Reste:

a) -OH,
b) Halogen,
c) $-C_{1-8}$-Alkoxy,
d) $-C_{1-6}$-Alkenyl,
e) $-CONR^5R^5$, worin R^5 unabhängig

i) -H,
ii) $-C_{1-8}$-Alkyl, das unsubstituiert oder mit einem oder mehreren der Reste R^7, Aryl oder heterocyclischer Rest, wie nachstehend definiert, substituiert ist, wobei der Arylrest unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist,
iii) Aryl, das unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist, oder
iv) ein wie nachstehend definierter heterocyclischer Rest ist, der unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist,

f) $-COOR^6$, worin R^6

i) -H,
ii) $-C_{1-8}$-Alkyl, das unsubstituiert oder mit einem oder mehreren der Reste R^7 oder Aryl substituiert ist,
wobei der Arylrest unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist, oder iii) Aryl, das unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist, ist,

g) $-S(O)_p-R^5$, worin p wie oben definiert ist,
h) $-N(R^5)_2$,
i) Aryl, das unsubstituiert oder mit einem oder mehreren der Reste Aryl, R^7 oder R^9 substituiert ist,
j) Heterocyclus, der unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist,
k) $-C_{3-10}$-Cycloalkyl, wie z.B. Cyclohexyl, Norbornyl oder Adamantyl, das unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist, oder
l) $-CONR^8-CO-NHR^8$, worin R^8 -H, $-C_{1-8}$-Alkyl, Benzyl oder Cyclohexyl ist, oder

2) Aryl, das unsubstituiert oder mit einem oder mehreren der Reste Aryl, R^7 oder R^9 substituiert ist, oder
3) Heterocyclus oder $-C_{3-10}$-Cycloalkyl, wobei jeder dieser Reste unsubstituiert oder mit einem oder meh-

reren der Reste R^7 oder R^9 substituiert ist,

R^7 1) -OH,
2) -C_{1-3}-Alkoxy,
3) -CN,
4) -$COOR^6$,
5) -C_{1-8}-Alkyl-$COOR^6$,
6) -NO_2 oder
7) -Halogen und
8) Amino, Mono-C_1-C_4-alkylamino, Di-C_1-C_4-alkylamino ist,

R^9 1) -C_{1-8}-Alkyl, das unsubstituiert oder mit einem oder mehreren der Reste Aryl oder R^7 substituiert ist,
2) -CO-A, -C_{1-8}-Alkyl-CO-A, -NHCO-A oder -$S(O)_p$-A,
worin p wie oben definiert ist, und A

a) -H,
b) -C_{1-8}-Alkyl, das unsubstituiert oder substituiert ist mit einem oder mehreren der Reste

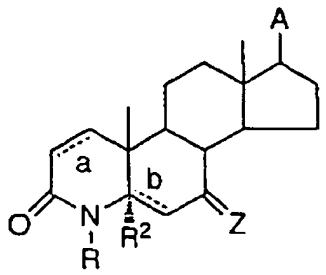
i) -R^7 oder
ii) Aryl, das unsubstituiert oder mit dem Rest R^7 oder mehreren davon substituiert ist, oder

c) Aryl, das unsubstituiert oder mit dem Rest R^7 oder mehreren davon substituiert ist, ist,

3) -NHCO-Heterocyclus,
4) -$N(R^{10})_2$ oder -$CON(R^{10})_2$, worin R^{10} unabhängig -H, Heterocyclus oder -A ist,
5) -NHCO-$(CH_2)_q$-CO-Q, worin q 1-4 und Q -$N(R^{10})_2$ oder -OR^{10} ist, ist,

wobei der Ausdruck Heterocyclus oder heterocyclischer Rest, so wie er hier verwendet wird, außer wenn angegeben, einen stabilen 5- bis 7gliedrigen monocyclischen heterocyclischen Ring bedeutet, der entweder gesättigt oder ungesättigt ist und aus Kohlenstoffatomen und ein bis drei Heteroatomen, ausgewählt aus der Gruppe, bestehend aus N, O und S, besteht, und worin die Stickstoff- und Schwefelheteroatome gegebenenfalls oxidiert und das Stickstoffheteroatom gegebenenfalls quaternisiert sein können/kann, und irgendeine bicyclische Gruppe umfaßt, bei der irgendeiner der oben definierten heterocyclischen Ringe an einen Benzolring kondensiert ist, wobei der heterocyclische Ring an irgendein Heteroatom oder Kohlenstoffatom gebunden sein kann, was zur Bildung einer stabilen Struktur führt, und pharmazeutisch annehmbare Salze davon.

2. Die Verbindung nach Anspruch 1 der Formel



worin: Z wie in Anspruch 1 definiert ist,
worin a und b beide Einfachbindungen sind und R^2 Wasserstoff ist, oder a eine Doppelbindung ist, b eine Einfachbindung ist und R^2 Wasserstoff ist, oder a eine Einfachbindung ist, b eine Doppelbindung ist und R^2 fehlt,

A -$(CHR^1)_n$-XR^4 ist,
n 1-10 ist,
X -O- oder -$S(O)_p$- ist, worin p null, 1 oder 2 ist, und

R^1 -H, Aryl oder -C_{1-3}-Alkyl ist, unsubstituiert oder substituiert mit C_{6-10}-Aryl,
R -H, Methyl oder Ethyl ist,
R^4 ist

1) -C_{1-20}-Alkyl, das unsubstituiert oder substituiert ist mit einem oder mehreren der Reste

a) -OH,
b) Halogen,
c) -C_{1-8}-Alkoxy,
d) -C_{1-6}-Alkenyl,
e) -$CONR^5R^5$, worin R^5 unabhängig

i) -H,
ii) -C_{1-8}-Alkyl, das unsubstituiert oder mit einem oder mehreren der Reste R^7, Aryl oder heterocyclischer Rest substituiert ist, wobei der Arylrest unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist,
iii) Aryl, das unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist, oder
iv) ein heterocyclischer Rest ist, der unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist,

f) -$COOR^6$, worin R^6

i) -H,
ii) -C_{1-8}-Alkyl, das unsubstituiert oder mit einem oder mehreren der Reste R^7 oder Aryl substituiert ist,
wobei der Arylrest unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist, oder
iii) Aryl, das unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist, ist,

g) -$S(O)_p$-R^5, worin p wie oben definiert ist,
h) -$N(R^5)_2$,
i) Aryl, das unsubstituiert oder mit einem oder mehreren der Reste Aryl, R^7 oder R^9 substituiert ist,
j) Heterocyclus, der unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist,
k) -C_{3-10}-Cycloalkyl, wie z.B. Cyclohexyl, Norbornyl oder Adamantyl, das unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist, oder
l) -$CONR^8$-CO-NHR^8, worin R^8 -H, -C_{1-8}-Alkyl, Benzyl oder Cyclohexyl ist, oder

2) Aryl, das unsubstituiert oder mit einem oder mehreren der Reste Aryl, R^7 oder R^9 substituiert ist, oder
3) Heterocyclus oder -C_{3-10}-Cycloalkyl, wobei jeder dieser Reste unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist,

R^7 1) -OH, 2) -C_{1-3}-Alkoxy,
3) -CN,
4) -$COOR^6$,
5) -C_{1-8}-Alkyl-$COOR^6$,
6) -NO_2 oder
7) -Halogen und
8) Amino, Mono-C_1-C_4-alkylamino, Di-C_1-C_4-alkylamino ist,

R^9 1) -C_{1-8}-Alkyl, das unsubstituiert oder mit einem oder mehreren der Reste Aryl oder R^7 substituiert ist,
2) -CO-A, -C_{1-8}-Alkyl-CO-A, -NHCO-A oder -$S(O)_p$-A, worin p wie oben definiert ist, und A

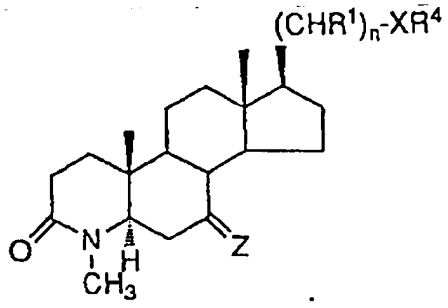
a) -H,
b) -C_{1-8}-Alkyl, das unsubstituiert oder substituiert ist mit einem oder mehreren der Reste

i) -R^7 oder
ii) Aryl, das unsubstituiert oder mit dem Rest R^7 oder mehreren davon substituiert ist, oder

c) Aryl, das unsubstituiert oder mit dem Rest R^7 oder mehreren davon substituiert ist, ist,

3) -NHCO-Heterocyclus,
4) $-N(R^{10})_2$ oder $-CON(R^{10})_2$, worin R^{10} unabhängig -H, Heterocyclus oder -A ist,
5) $-NHCO-(CH_2)_q-CO-Q$, worin q 1-4 und Q $-N(R^{10})_2$ oder $-OR^{10}$ ist, ist.

3. Die Verbindung nach Anspruch 2 mit der Strukturformel:



4. Die Verbindung nach Anspruch 3, worin R^4 $-C_{1-20}$-Alkyl ist, das unsubstituiert oder substituiert ist mit einem oder mehreren der Reste -OH, Halogen, $-C_{1-8}$-Alkoxy, $-C_{1-6}$-Alkenyl, $-S(O)_p-R^5$, $-N(R^5)_2$, Aryl, unsubstituiert oder substituiert mit einem oder mehreren der Reste Aryl, R^7 oder R^9, Heterocyclus, unsubstituiert oder substituiert mit einem oder mehreren der Reste R^7 oder R^9, oder $-C_{3-10}$-Cycloalkyl, unsubstituiert oder substituiert mit einem oder mehreren der Reste R^7 oder R^9.

5. Die Verbindung nach Anspruch 3, worin R^4 $-C_{1-20}$-Alkyl ist, das mit $-CONR^5R^5$, $-COOR^6$ oder $-CONR^8CONHR^8$ substituiert ist.

6. Die Verbindung nach Anspruch 3, worin R^4 Aryl, das unsubstituiert oder mit einem oder mehreren der Reste Aryl, R^7 oder R^9 substituiert ist, Heterocyclus, der unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist, oder $-C_{3-10}$-Cycloalkyl, das unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist, ist.

7. Die Verwendung einer Verbindung nach Anspruch 1 zur Herstellung eines Medikaments zur Behandlung der hyperandrogenen Zustände von Akne, androgener Alopezie, Alopezie des männlichen Typs, weiblichem Hirsutismus, benigner Prostatahyperplasie, Prostatitis, zur Behandlung und Prävention von Prostatakarzinom.

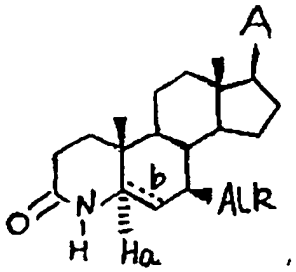
8. Die wie in Anspruch 7 beanspruchte Verwendung, worin die Verbindung ein 5α-Reduktase-1-Inhibitor ist.

9. Die wie in Anspruch 7 beanspruchte Verwendung, worin die Verbindung ein 5α-Reduktase-2-Inhibitor ist.

10. Die wie in Anspruch 7 beanspruchte Verwendung, worin die Verbindung ein zweifacher Inhibitor sowohl für 5α-Reduktase 1 als auch für 5α-Reduktase 2 ist.

11. Eine pharmazeutische Zusammensetzung, die eine therapeutisch wirksame Menge der Verbindung nach Anspruch 1 in einem pharmazeutisch annehmbaren Vehikel dafür enthält.

12. Ein Verfahren zur Synthese einer Verbindung der Formel



worin

R ausgewählt ist aus Wasserstoff, Methyl oder Ethyl, die gestrichelten Linien a, b, e Doppelbindungen bedeuten, die vorliegend können, mit der Maßgabe, daß, wenn Doppelbindung b vorliegt, das 5α-Wasserstoff, Ha, dann nicht vorhanden ist, worin

Alk C_1-C_4-Alkyl, C_2-C_4-Alkenyl, $-CH_2COOH$, Hydroxy, Carboxy, $COOC_1$-C_4-Alkylester ist,

A $-(CHR^1)_n-XR^4$ ist,

n 1-10 ist,

X -O- oder $-S(O)_p-$ ist, worin p null, 1 oder 2 ist, und

R^1, wenn n größer als 1 ist, gleich oder verschieden sein kann und -H, Aryl oder $-C_{1-3}$-Alkyl, unsubstituiert oder substituiert mit C_6-C_{10}-Aryl, ist,

R -H, Methyl oder Ethyl ist,

R^4 ist

1) Wasserstoff oder $-C_{1-20}$-Alkyl, das unsubstituiert oder substituiert ist mit einem oder mehreren der Reste:

a) -OH,
b) Halogen,
c) $-C_{1-8}$-Alkoxy,
d) $-C_{1-6}$-Alkenyl,
e) $-CONR^5R^5$, worin R^5 unabhängig

i) -H,
ii) $-C_{1-8}$-Alkyl, das unsubstituiert oder mit einem oder mehreren der Reste R^7, Aryl oder heterocyclischer Rest, wie nachstehend definiert, substituiert ist,
wobei der Arylrest unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist,
iii) Aryl, das unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist, oder
iv) ein wie nachstehend definierter heterocyclischer Rest ist, der unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist,

f) $-COOR^6$, worin R^6

i) -H,
ii) $-C_{1-8}$-Alkyl, das unsubstituiert oder mit einem oder mehreren der Reste R^7 oder Aryl substituiert ist,
wobei der Arylrest unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist, oder iii) Aryl, das unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist, ist,

g) $-S(O)_p-R^5$, worin p wie oben definiert ist,
h) $-N(R^5)_2$,
i) Aryl, das unsubstituiert oder mit einem oder mehreren der Reste Aryl, R^7 oder R^9 substituiert ist,

j) Heterocyclus, der unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist,
k) -C_{3-10}-Cycloalkyl, das unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist, oder
l) -$CONR^8$-CO-NHR^8, worin R^8 -H, -C_{1-8}-Alkyl, Benzyl oder Cyclohexyl ist, oder

2) Aryl, das unsubstituiert oder mit einem oder mehreren der Reste Aryl, R^7 oder R^9 substituiert ist, oder
3) Heterocyclus oder -C_{3-10}-Cycloalkyl, wobei jeder dieser Reste unsubstituiert oder mit einem oder mehreren der Reste R^7 oder R^9 substituiert ist,

R^7 1) -OH,
2) -C_{1-3}-Alkoxy,
3) -CN,
4) -$COOR^6$,
5) -C_{1-8}-Alkyl-$COOR^6$,
6) -NO_2 oder
7 -Halogen und
8) Amino, Mono-C_1-C_4-alkylamino, Di-C_1-C_4-alkylamino ist,

R^9 1) -C_{1-8}-Alkyl, das unsubstituiert oder mit einem oder mehreren der Reste Aryl oder R^7 substituiert ist,
2) -CO-A, -C_{1-8}-Alkyl-CO-A, -NHCO-A oder -$S(O)_p$-A,
worin p wie oben definiert ist, und A

a) -H,
b) -C_{1-8}-Alkyl, das unsubstituiert oder substituiert ist mit einem oder mehreren der Reste

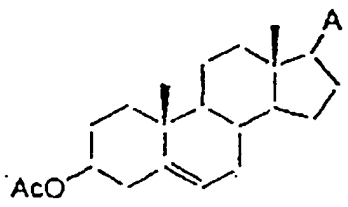
i) -R^7 oder
ii) Aryl, das unsubstituiert oder mit dem Rest R^7 oder mehreren davon substituiert ist, oder

c) Aryl, das unsubstituiert oder mit dem Rest R^7 oder mehreren davon substituiert ist, ist,

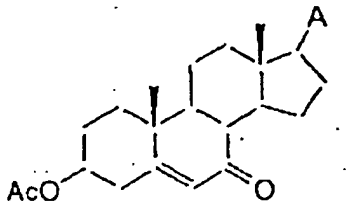
3) -NHCO-Heterocyclus,
4) -$N(R^{10})_2$ oder -$CON(R^{10})_2$, worin R^{10} unabhängig -H, Heterocyclus oder -A ist,
5) -NHCO-$(CH_2)_q$-CO-Q, worin q 1-4 und Q -$N(R^{10})_2$ oder -OR^{10} ist, ist,

wobei der Ausdruck Heterocyclus oder heterocyclischer Rest, so wie er hier verwendet wird, außer wenn angegeben, einen stabilen 5- bis 7gliedrigen monocyclischen heterocyclischen Ring bedeutet, der entweder gesättigt oder ungesättigt ist und aus Kohlenstoffatomen und ein bis drei Heteroatomen, ausgewählt aus der Gruppe, bestehend aus N, O und S, besteht, und worin die Stickstoff- und Schwefelheteroatome gegebenenfalls oxidiert und das Stickstoffheteroatom gegebenenfalls quaternisiert sein können/kann, und irgendeine bicyclische Gruppe umfaßt, bei der irgendeiner der oben definierten heterocyclischen Ringe an einen Benzolring kondensiert ist, wobei der heterocyclische Ring an irgendein Heteroatom oder Kohlenstoffatom gebunden sein kann, was zur Bildung einer stabilen Struktur führt,
wobei das Verfahren die Schritte umfaßt:

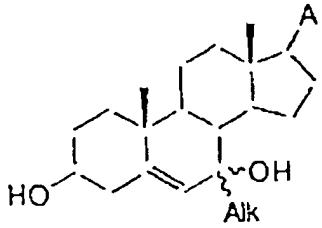
(a) Oxidieren einer Verbindung der Formel



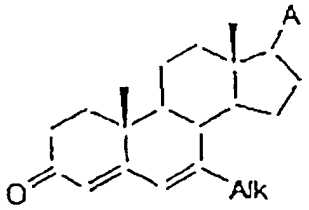
um das entsprechende Keton der Formel



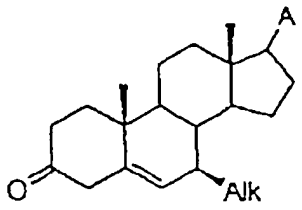
zu erzeugen,
(b) Alkylieren des Produkts aus (a), um das entsprechende Alkyl-Hydroxy-Addukt der Formel



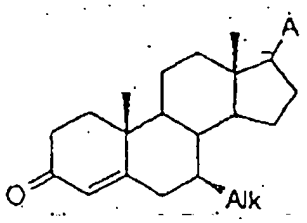
zu erzeugen,
(c) Oxidieren des Produkts aus (b), um ein Dien der Formel



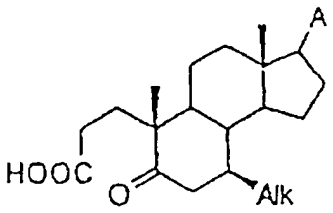
zu erzeugen,
(d) Reduzieren des Produkts aus (c), um eine Verbindung der Formel



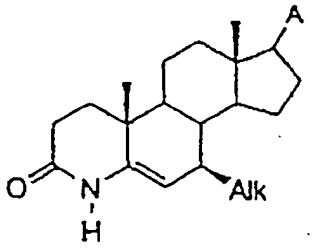
zu erzeugen,
e) Isomerisieren des Produkts aus (d), um das 4-en der Formel



zu erzeugen,
(f) Spalten des A-Rings in dem Produkt aus (e), um eine Secosäure der Formel



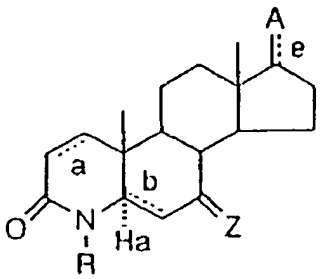
zu erzeugen, und
(g) Schließen des Rings des Produkts, um eine 4-Alkyl-4-azaandrost-5-en-Verbindung der Formel



zu erzeugen, gefolgt von wahlweiser selektiver Reduktion der 5-Doppelbindung.

Revendications

1. Composé de formule



dans laquelle

R est choisi parmi un atome d'hydrogène, le groupe méthyle ou éthyle; les traits pointillés a, b, e indiquent des doubles liaisons qui peuvent être présentes, étant entendu que si la double liaison b est présente, l'atome d'hydrogène en 5α, Ha, n'est pas présent;

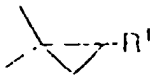
Z est choisi parmi

1) le groupe oxo,

2) l'atome d'hydrogène a et un substituant β choisi parmi un groupe alkyle en C_1-C_4, alcényle en C_2-C_4, $-CH_2COOH$, hydroxy, carboxy, ester COO-alkyle(C_1-C_4), un groupe $OCONR^1R^2$, dans lequel R^1 et R^2 représentent indépendamment H ou un radical alkyle en C_1-C_4, phényle, benzyle, et dans lequel R^1 et R^2 peuvent former ensemble, avec l'atome d'azote, un cycle hétérocyclique saturé à 5-6 chaînons, comportant éventuellement un autre hétéroatome, un groupe O-alkyle en C_1-C_4, O-cycloalkyle en C_3-C_6, $-OCOCH_3$, un atome d'halogène, un groupe halogénoalkyle en C_1-C_2 ou trifluorométhyle, un groupe cycloalkyle en C_3-C_6;

3) un groupe $=CH-R^1$, dans lequel R^1 est H ou un radical alkyle en C_1-C_4;

4) un groupe spirannique



dans lequel R^1 est H ou un groupe alkyle en C_1-C_4; et A est un groupe $-(CHR^1)_n-XR^4$;
n va de 1 à 10;
X représente -O- ou $-S(O)_p-$,
p étant O, 1 ou 2; et les radicaux R^1 peuvent être identiques ou différents lorsque n est supérieur à 1, et représentent -H ou un groupe aryle ou alkyle en C_1-C_3 non substitué ou substitué par un radical aryle en C_6-C_{10};
R est -H ou le groupe méthyle ou éthyle;
R^4 est

1) un atome d'hydrogène ou un groupe alkyle en C_1-C_{20}, non substitué ou portant un ou plusieurs substituants choisis parmi:

a) -OH,
b) des atomes d'halogène,
c) des groupes alcoxy en C_1-C_8,
d) des groupes alcényle en C_1-C_6,
e) $-CONR^5R^5$, R^5 étant indépendamment

i) -H,
ii) un groupe alkyle en C_1-C_8 non substitué ou substitué par un ou plusieurs radicaux R^7, aryle ou hétérocycliques définis ci-dessous, les radicaux aryle étant non substitués ou substitués par un ou plusieurs radicaux R^7 ou R^9,
iii) un groupe aryle non substitué ou substitué par un ou plusieurs radicaux R^7 ou R^9, ou
iv) un groupe hétérocyclique, défini ci-dessous, non substitué ou substitué par un ou plusieurs radicaux R^7 ou R^9,

f) $-COOR^6$, R^6 représentant

i) -H,
ii) un groupe alkyle en C_1-C_8 non substitué ou substitué par un ou plusieurs radicaux R^7 ou aryle, le groupe aryle étant non substitué ou substitué par un ou plusieurs radicaux R^7 ou R^9, ou
iii) un groupe aryle non substitué ou substitué par un ou plusieurs radicaux R^7 ou R^9,

g) $-S(O)_p-R^5$, p étant tel que défini plus haut,
h) $-N(R^5)_2$,
i) un groupe aryle non substitué ou substitué par un ou plusieurs radicaux aryle, R^7 ou R^9,
j) un groupe hétérocyclique non substitué ou substitué par un ou plusieurs radicaux R^7 ou R^9,
k) un groupe cycloalkyle en C_3-C_{10}, tel que cyclohexyle, norbornyle ou adamantyle, non substitué ou substitué par un ou plusieurs radicaux R^7 ou R^9, ou
l) $-CONR^8-CO-NHR^8$, R^8 représentant H ou un groupe alkyle en C_1-C_8, benzyle ou cyclohexyle; ou

2) un groupe aryle non substitué ou substitué par un ou plusieurs radicaux aryle, R^7 ou R^9, ou
3) un groupe hétérocyclique ou cycloalkyle en C_3-C_{10}, l'un et l'autre non substitués ou substitués par un ou plusieurs radicaux R^7 ou R^9;

R^7 est

1) -OH,
2) un groupe alcoxy en C_1-C_3,
3) -CN,
4) $-COOR^6$,
5) un groupe alkyl (C_1-C_8)-$COOR^6$,
6) $-NO_2$, ou
7) un atome d'halogène; et
8) un groupe amino, monoalkyl(C_1-C_4)amino ou dialkyl-(C_1-C_4)amino;

R^9 est

1) un groupe alkyle en C_1-C_8, non substitué ou substitué par un ou plusieurs radicaux aryle ou R^7,
2) un groupe -CO-A, -alkyl(C_1-C_8)-CO-A, -NHCO-A ou $-S(O)_p-A$,
p étant tel que défini plus haut et A étant

a) -H,
b) un groupe alkyle en C_1-C_8, non substitué ou portant un ou plusieurs substituants choisis parmi

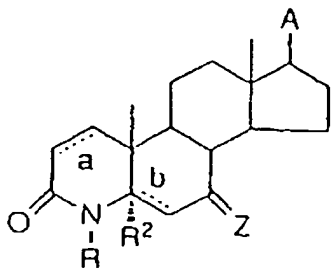
i) $-R^7$ et
ii) un groupe aryle non substitué ou substitué par un ou plusieurs radicaux R^7, ou

c) un groupe aryle non substitué ou substitué par un ou plusieurs radicaux R^7,

3) un groupe -NHCO-hétérocycle,
4) un groupe $-N(R^{10})_2$ ou $-CON(R^{10})_2$, R^{10} étant indépendamment -H, un hétérocycle ou -A,
5) un groupe $-NHCO-(CH_2)_q-CO-Q$, q allant de 1 à 4 et Q étant $N(R^{10})_2$ ou $-OR^{10}$;

le terme hétérocycle ou hétérocyclique, tel qu'utilisé ici, à moins d'indication contraire, représente un cycle monocyclique hétérocyclique stable à 5-7 chaînons, qui est soit saturé, soit insaturé, et qui consiste en atomes de carbone et en 1 à 3 hétéroatomes choisis dans le groupe constitué par N, O et S, et dans lequel les hétéroatomes d'azote et de soufre peuvent éventuellement être oxydés, et l'hétéroatome d'azote peut éventuellement être rendu quaternaire, et comprenant tout groupe bicyclique dans lequel l'un quelconque des cycles hétérocycliques définis ci-dessus est soudé à un noyau benzénique, le cycle hétérocyclique pouvant être lié au niveau d'un atome de carbone ou hétéroatome quelconque, ce qui entraîne la création d'une structure stable, et sels pharmaceutiquement acceptables de ce composé.

2. Composé selon la revendication 1, de formule



dans laquelle

Z est tel que défini dans la revendication 1;
a et b sont l'un et l'autre une liaison simple et R^2 est un atome d'hydrogène, ou
a est une double liaison, b est une liaison simple et R^2 est absent;
A est $-(CHR^1)_n-XR^4$;
n va de 1 à 10;
X est -O- ou $-S(O)_p-$, p étant égal à 0, 1 ou 2; et

R^1 est -H ou un groupe aryle ou alkyle en C_1-C_3 non substitué ou substitué par un radical aryle en C_6-C_{10};
R est -H ou le groupe méthyle ou éthyle;
R^4 est

1) un groupe alkyle en C_1-C_{20}, non substitué ou portant un ou plusieurs substituants choisis parmi

a) -OH,
b) des atomes d'halogène,
c) des groupes alcoxy en C_1-C_8,
d) des groupes alcényle en C_1-C_6,
e) $-CONR^5R^5$, R^5 étant indépendamment

i) -H,
ii) un groupe alkyle en C_1-C_8 non substitué ou substitué par un ou plusieurs radicaux R^7, aryle ou hétérocycliques, les groupes aryle étant non substitués ou substitués par un ou plusieurs radicaux R^7 ou R^9,
iii) un groupe aryle non substitué ou substitué par un ou plusieurs radicaux R^7 ou R^9, ou
iv) un hétérocycle non substitué ou substitué par un ou plusieurs radicaux R^7 ou R^9,

l) $-COOR^6$, R^6 étant

i) -H,
ii) un groupe alkyle en C_1-C_8 non substitué ou portant un ou plusieurs substituants choisis parmi R^7 ou des groupes aryle, les groupes aryle étant non substitués ou substitués par un ou plusieurs radicaux R^7 ou R^9, ou
iii) des groupes aryle non substitués ou substitués par un ou plusieurs radicaux R^7 ou R^9,

g) $-S(O)_p-R^5$, p étant tel que défini plus haut,
h) $N(R^5)_2$,
i) un groupe aryle non substitué ou substitué par un ou plusieurs radicaux aryle, R^7 ou R^9,
j) un hétérocycle non substitué ou substitué par un ou plusieurs radicaux R^7 ou R^9,
k) un groupe cycloalkyle en C_3-C_{10}, tel que cyclohexyle, norbornyle ou adamantyle, non substitué ou substitué par un ou plusieurs radicaux R^7 ou R^9, ou

1) $-CONR^8-CO-NHR^8$, R^8 étant H ou un groupe alkyle en C_1-C_8, benzyle ou cyclohexyle; ou
2) un groupe aryle non substitué ou substitué par un ou plusieurs radicaux aryle, R^7 ou R^9, ou
3) un groupe hétérocyclique ou cycloalkyle en C_3-C_{10}, chacun non substitué ou substitué par un ou

plusieurs radicaux R^7 ou R^9;

R^7 est

1) -OH,
2) un groupe alcoxy en C_1-C_3,
3) -CN,
4) -$COOR^6$,
5) un groupe alkyl(C_1-C_8)-$COOR^6$,
6) -NO_2, ou
7) un atome d'halogène; et
8) un groupe amino, monoalkyl(C_1-C_4)amino ou dialkyl-(C_1-C_4)amino;

R^9 est

1) un groupe alkyle en C_1-C_8, non substitué ou substitué par un ou plusieurs radicaux aryle ou R^7,
2) un groupe -CO-A, -alkyl(C_1-C_8)-CO-A, -NHCO-A ou -$S(O)_p$-A, p étant tel que défini plus haut et A étant

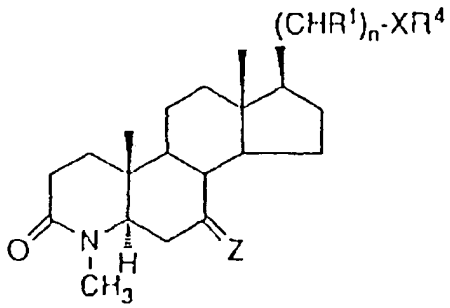
a) -H,
b) un groupe alkyle en C_1-C_8, non substitué ou portant un ou plusieurs substituants choisis parmi

I) -R^7 ou
II) un groupe aryle non substitué ou substitué par un ou plusieurs radicaux R^7, ou

c) un groupe aryle non substitué ou substitué par un ou plusieurs radicaux R^7,

3) un groupe -NHCO-hétérocycle,
4) un groupe -$N(R^{10})_2$ ou -$CON(R^{10})_2$, R^{10} étant indépendamment -H, un hétérocycle ou -A,
5) un groupe -NHCO-$(CH_2)_q$-CO-Q, q allant de 1 à 4 et Q étant un groupe -$N(R^{10})_2$ ou -OR^{10}.

3. Composé selon la revendication 2, correspondant à la formule développée:



4. Composé selon la revendication 3, dans lequel R^4 est un groupe alkyle en C_1-C_{20}, non substitué ou portant un ou plusieurs substituants choisis parmi des atomes d'halogène et des groupes -OH, alcoxy en C_1-C_8, alcényle en C_1-C_6, -$S(O)_p$-R^5, -$N(R^5)_2$, un groupe aryle non substitué ou substitué par un ou plusieurs radicaux aryle, R_7 ou R_9, un groupe hétérocyclique non substitué ou substitué par un ou plusieurs radicaux R^7 ou R^9, ou un groupe cycloalkyle en C_3-C_{10} non substitué ou substitué par un ou plusieurs radicaux R^7 ou R^9.

5. Composé selon la revendication 3, dans lequel R^4 est un groupe alkyle en C_1-C_{20} substitué par -$CONR^5R^5$, -$COOR^6$ ou -$CONR^8CONHR^8$.

6. Composé selon la revendication 3, dans lequel R^4 est un groupe aryle non substitué ou substitué par un ou plusieurs radicaux aryle, R^7 ou R^9, un groupe hétérocyclique non substitué ou substitué par un ou plusieurs radicaux

R^7 ou R^9, ou un groupe cycloalkyle en C_3-C_{10} non substitué ou substitué par un ou plusieurs radicaux R^7 ou R^9.

7. Utilisation d'un composé selon la revendication 1, pour la fabrication d'un médicament destiné au traitement des états hyperandrogéniques de l'acné, l'alopécie androgénique, l'alopécie séborrhéique masculine, l'hirsutisme féminin, l'hyperplasie bénigne de la prostate, la prostatite, le traitement et la prévention du cancer de la prostate.

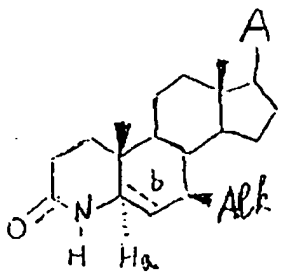
8. Utilisation selon la revendication 7, dans laquelle ledit composé est un inhibiteur de la 5α-réductase 1.

9. Utilisation selon la revendication 7, dans laquelle ledit composé est un inhibiteur de la 5α-réductase 2.

10. Utilisation selon la revendication 7, dans laquelle ledit composé est un double inhibiteur à la fois de la 5α-réductase 1 et de la 5α-réductase 2.

11. Composition pharmaceutique comprenant une quantité thérapeutiquement efficace d'un composé selon la revendication 1, dans un véhicule pharmaceutiquement acceptable pour celui-ci.

12. Procédé pour la synthèse d'un composé de formule



dans laquelle R est choisi parmi un atome d'hydrogène, le groupe méthyle ou éthyle; les traits pointillés a, b, e, indiquent des doubles liaisons qui peuvent être présentes, étant entendu que si la double liaison b est présente, l'atome d'hydrogène en 5α, Ha, n'est pas présent; Alk est un groupe alkyle en C_1-C_4, acényle en C_2-C_4, CH_2COOH, hydroxy, carboxy, ester COO-alkyle (C_1-C_4);

A est un groupe $-(CHR^1)_n-XR^4$;
n va de 1 à 10;
X représente -O- ou $-S(O)_p-$, p étant 0, 1 ou 2; et
les radicaux R^1 peuvent être identiques ou différents lorsque n est supérieur à 1, et représentent un groupe aryle ou alkyle en C_1-C_3 non substitué ou substitué par par un radical aryle en C_6-C_{10};
R est -H ou le groupe méthyle ou éthyle;
R^4 est

1) un atome d'hydrogène ou uy groupe alkyle en C_1-C_{20}, non substitué ou portant un ou plusieurs substituants choisis parmi:

a) -OH,
b) des atomes d'halogène,
c) des groupes alcoxy en C_1-C_8,
d) des groupes alcényle en C_1-C_6,
e) $-CONR^5R^5$, R^5 étant indépendamment

i) -H,
ii) un groupe alkyle en C_1-C_8 non substitué ou substitué par un ou plusieurs radicaux R^7, aryle ou hétérocycliques définis ci-dessous, les radicaux aryle étant non substitués ou substitués par un ou plusieurs radicaux R^7 ou R^9,
iii) un groupe aryle non substitué ou substitué par un ou plusieurs radicaux R^7 ou R^9, ou
iv) un groupe hétérocyclique, défini ci-dessous, non substitué ou substitué par un ou plusieurs

radicaux R^7 ou R^9,

f) $-COOR^6$, R^6 représentant

i) -H,
ii) un groupe alkyle en C_1-C_8 non substitué ou substitué par un ou plusieurs radicaux R^7 ou aryle, le groupe aryle étant non substitué ou substitué par un ou plusieurs radicaux R^7 ou R^9, ou
iii) un groupe aryle non substitué ou substitué par un ou plusieurs radicaux R^7 ou R^9,

g) $-S(O)_p-R^5$, p étant tel que défini plus haut,
h) $-N(R^5)_2$,
i) un groupe aryle non substitué ou substitué par un ou plusieurs radicaux aryle, R^7 ou R^9,
j) un groupe hétérocyclique non substitué ou substitué par un ou plusieurs radicaux R^7 ou R^9,
k) un groupe cycloalkyle en C_3-C_{10}, non substitué ou substitué par un ou plusieurs radicaux R^7 ou R^9, ou
l) $-CONR^8-CO-NHR^8$, R^8 représentant H ou un groupe alkyle en C_1-C_8, benzyle ou cyclohexyle; ou

2) un groupe aryle non substitué ou substitué par un ou plusieurs radicaux aryle, R^7 ou R^9, ou
3) un groupe hétérocyclique ou cycloalkyle en C_3-C_{10}, l'un et l'autre non substitués ou substitués par un ou plusieurs radicaux R^7 ou R^9;

R^7 est

1) -OH,
2) un groupe alcoxy en C_1-C_3,
3) -CN,
4) $-COOR^6$,
5) un groupe alkyl(C_1-C_8)-$COOR^6$,
6) $-NO_2$, ou
7) un atome d'halogène; et
8) un groupe amino, monoalkyl(C_1-C_4)amino ou dialkyl-(C_1-C_4) amino;

R^9 est

1) un groupe alkyle en C_1-C_8, non substitué ou substitué par un ou plusieurs radicaux aryle ou R^7,
2) un groupe -CO-A, -alkyl(C_1-C_8)-CO-A, -NHCO-A ou $-S(O)_p$-A, p étant tel que défini plus haut et A étant

a) -H,
b) un groupe alkyle en C_1-C_8, non substitué ou portant un ou plusieurs substituants choisis parmi

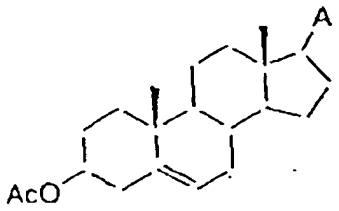
i) $-R^7$ et
ii) un groupe aryle non substitué ou substitué par un ou plusieurs radicaux R^7, ou

c) un groupe aryle non substitué ou substitué par un ou plusieurs radicaux R^7,

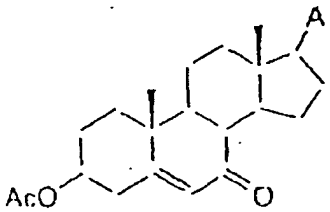
3) un groupe -NHCO-hétérocycle,
4) un groupe $-N(R^{10})_2$ ou $-CON(R^{10})_2$, R^{10} étant indépendamment -H, un hétérocycle ou -A,
5) un groupe $-NHCO-(CH_2)_q-CO-Q$, q allant de 1 à 4 et Q étant $-N(R^{10})_2$ ou $-OR^{10}$;

le terme hétérocycle ou hétérocyclique, tel qu'utilisé ici, à moins d'indication contraire, représente un cycle monocyclique hétérocyclique stable à 5-7 chaînons, qui est soit saturé, soit insaturé, et qui consiste en atomes de carbone et en 1 à 3 hétéroatomes choisis dans le groupe constitué par N, O et S, et dans lequel les hétéroatomes d'azote et de soufre peuvent éventuellement être oxydés, et l'hétéroatome d'azote peut éventuellement être rendu quaternaire, et comprenant tout groupe bicyclique dans lequel l'un quelconque des cycles hétérocycliques définis ci-dessus est soudé à un noyau benzénique, le cycle hétérocyclique pouvant être lié au niveau d'un atome de carbone ou hétéroatome quelconque, ce qui entraîne la création d'une structure stable, procédé comprenant les étapes suivantes:

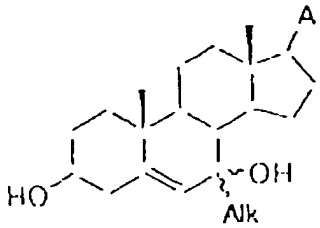
(a) oxydation d'un composé de formule



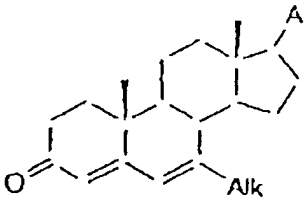
pour l'obtention de la cétone correspondante de formule



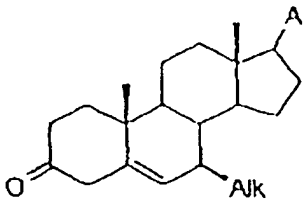
(b) alkylation du produit de (a) pour l'obtention de l'adduct alkyl-hydroxy correspondant, de formule



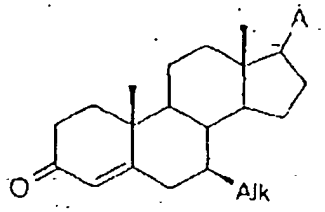
(c) oxydation du produit de (b) pour l'obtention d'un diène de formule



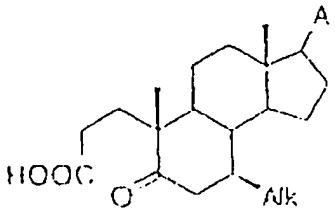
(d) réduction du produit de (c) pour l'obtention d'un composé de formule



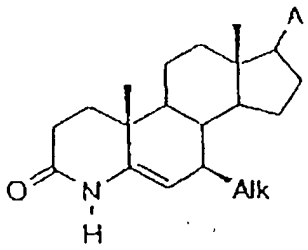
(e) isomérisation du produit de (d) pour l'obtention du 4-ène de formule



(f) coupure du cycle A dans le produit de (e), pour l'obtention d'un acide seco de formule



(g) fermeture du cycle du produit, pour l'obtention d'un produit de type 4-alkyl-4-aza-androst-5-ène de formule



suivie d'une éventuelle réduction sélective de la double liaison en position 5.